special report

CHILDHOOD
THE ROAD AHEAD

Help for hurts
The long shadow of childhood trauma

Grown up
Easing child patients into adulthood

Liftoff
Rocket science meets medicine

ZZZs
The Rx for teens

Jimmy Carter
His final campaign

plus

Viruses ‘R’ Us
Are we infected as embryos?

What’s your emergency?
Inside India’s groundbreaking ambulance system
BAD FOR THE BONE
THE TOLL OF CHILDHOOD CHRONIC DISEASE

Mary Leonard, MD, is pointing at a spine MRI scan of a young adult who had a bone marrow transplant in childhood. “That vertebra is compressed,” says Leonard, a professor of pediatrics and of medicine who serves as an associate dean for maternal and child health research. “These patients who are in their teens or early 20s have little-old-lady kinds of fractures.” • Preventing early osteoporotic fractures in those who have withstood childhood chronic diseases is a central aim of Leonard’s research program. She and her colleagues have documented abnormal bone structure, muscle mass and muscle strength in children and teens with conditions ranging from cancer to Crohn’s disease to organ transplantation.

Immobility, inflammation, malabsorption of nutrients and treatment with radiation or steroids can all pose threats to developing bones. • “We believe that once you go through puberty, you’re not getting that bone back,” Leonard says. “I feel like we’ve described and described the problem, and now we need to do clinical trials to see what we can do to improve bone health in these patients. We just want to make sure they go into adulthood with the best, strongest skeleton possible — with bones to last a lifetime.”

Clinical trials could assess the efficacy of exercise programs, compare kidney-transplant patients on a steroid-free protocol with those who are given steroids and, eventually, test pharmaceutical interventions. In a new Stanford research center on Arastradero Road in Palo Alto, both kids with chronic diseases and healthy control subjects will undergo three assessments: a muscle-strength exam; a full-body DXA scan to quantify bone, muscle and fat; and ankle and wrist scans in the latest-generation XtremeCT machine. The total radiation dose from the three tests, Leonard says, is less than a week of background radiation exposure from living on Earth.

The XtremeCT is one of 10 in the United States, and one of only two being used to assess children with chronic diseases. “Its name is the HR-pQCT, but we call it the hokey-pokey machine, because you put your right arm in; you put your right arm out,” says Leonard. As long as you don’t actually shake it all about — children under 5, it seems, are too wiggly to be scanned — the high-resolution CT yields a fine-grained look at bone structure in those arms and legs. “DXA bone density scans tell you how much bone is there, but don’t tell you enough about bone quality — its thickness, porosity and micro-architecture,” she says. By comparing before-and-after scans from the HR-pQCT machine, “we can really look at what the treatment is doing to bone structure and strength.”

Leonard sees two implications of her work. First, some children with chronic diseases may need to be treated more aggressively before and during puberty, to improve their overall health and enable them to build more bone. “If you wait to treat the Crohn’s until their bones are done developing, or if they don’t get their kidney transplant until their bones are done developing, that window of opportunity may be lost.” Second, as life expectancy improves for children with rare and once-fatal conditions, physicians need to anticipate the lasting effects of their illness and treatment.

“As patients with complex congenital heart disease or cancer are surviving well into adulthood, the focus of research has to shift from improving survival to understanding some of the long-term complications,” Leonard says. “And osteoporosis and fractures are part of it.” — KATHY ZONANA
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WE MAY BE INFECTED — AND PROTECTED — FROM OUR EARLIEST DAYS OF DEVELOPMENT

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Aside from the bruises, scrapes and occasional broken bones that accompany childhood, most children — thankfully — are quite healthy. They see the inside of a doctor's office for annual wellness checkups and vaccines, but are otherwise unfamiliar with treatment in a hospital. They don’t know what it feels like to have an I.V. inserted, and they haven’t experienced the disappointment of missing yet another season of soccer because they’re too sick to run up and down the field. But for those children who are not so healthy, the consequences can be devastating.

Childhood diseases are crippling for the children and families they affect. Here at Stanford Medicine, we are exploring the tremendous potential of stem cells and gene therapy to find definitive cures to rare childhood diseases for which there are currently no therapeutic options. We are seeking to cure the incurable disease.

The work of Maria Grazia Roncarolo, a pediatric immunologist and the co-director of Stanford’s Institute for Stem Cell Biology and Regenerative Medicine, presents some especially inspiring examples. Under her leadership, Lucile Packard Children’s Hospital Stanford performs blood stem cell transplants to cure children with genetic diseases and cancer. And she expects to begin testing several experimental stem cell gene therapies in patients next year. It has never been more exciting to see Stanford’s strengths in basic research translated to new medical therapies.

There is other hopeful news for stem cell and gene therapy on the horizon. A treatment for severe combined immune deficiency that Dr. Roncarolo developed while the director of the Telethon Institute for Gene Therapy and scientific director of the San Raffaele Scientific Institute in Italy is currently under review for marketing authorization at the European Medicines Agency — Europe’s equivalent of our Food and Drug Administration. If approved, the treatment for the condition, more widely known as “bubble boy disease,” would be the first stem cell gene therapy to be authorized by a major medical regulatory agency. (A second stem cell gene therapy for a lethal metabolic disease, also developed by Dr. Roncarolo’s team, will soon be submitted to the FDA for registration and marketing authorization.) Approval would mean the treatments are available like any other treatment and covered by insurance.

Treatments like these hold enormous promise and could usher in an era in which genetically modified stem cells are used to treat or cure a wide range of human diseases, presenting real hope for children whose lives had been devoid of it.

Now, Roncarolo and her team are busy researching cures for other congenital immune disorders and developing methods that could lead to stem cell treatments for a variety of diseases. And although we have a long bridge to cross between research and application, we eagerly look forward to a future where scraped knees are all that interrupt the boundless energy and hope of childhood.

Sincerely,
Lloyd Minor, MD
Carl and Elizabeth Naumann Dean of the School of Medicine
Professor of Otolaryngology-Head & Neck Surgery
A whale of a mystery

OF THE 60 MAMMALS WHOSE GENOMES WERE COMPARED RECENTLY BY SCHOOL OF MEDICINE RESEARCHERS, only toothed whales, like dolphins and orcas, lack functional Mx genes — the source of key antiviral proteins that fight viruses such as HIV, measles and flu.

"Given how important the Mx genes seem to be in fighting off disease in humans and other mammals, it’s striking to see a species lose them both and go about its business for millions of years,” says Gill Bejerano, PhD, associate professor of developmental biology, of computer science and of pediatrics. He hypothesizes that the common ancestor of these mammals was subjected to a virus that exploited the Mx genes, and “their option was to lose both genes or die.”

Bejerano is the senior author of the study, published in the Proceedings of the National Academy of Sciences. The researchers hope others will investigate whether toothed whales’ immune systems are compromised — a possible explanation for recent die-offs — or whether they’ve developed compensatory mutations. Ultimately, this could lead to new treatments for human autoimmune disorders.

“We’re putting the genomic discovery out there, and we hope immunologists will follow up on it,” says Bejerano. “This is an amazing time to be a thoughtful genomicist. And hopefully, we’ve helped make it a slightly better time to be a toothed whale.”
Native ties

Kennewick Man, an 8,500-year-old adult skeleton found in Washington state in 1996, is more closely related to Native American populations than to any other population in the world, according to a new analysis. The finding challenges a 2014 study concluding, based on anatomical data, that Kennewick Man was more related to indigenous Japanese or Polynesian peoples.

The new study compared genetic sequences obtained from a bone in the skeleton's hand to worldwide genomic data, finding that Kennewick Man is most akin to modern Native Americans. Although the researchers couldn’t assign him to a particular tribe, they say he is closely related to members of the Confederated Tribes of the Colville Reservation in Washington.

Native Americans in the Pacific Northwest have long held that the skeleton, which they call the Ancient One, is that of an ancestor. The new findings, published in June in Nature, are expected to reignite a legal battle in which five tribes have requested repatriation of the remains for reburial. Lead author and postdoctoral scholar Morten Rasmussen, PhD, started the study at the University of Copenhagen and completed it at Stanford, working with Carlos Bustamante, PhD, professor of genetics.

“Advances in DNA sequencing technology have given us important new tools for studying the great human diasporas and the history of indigenous populations,” says Bustamante. “Morten’s work aligns beautifully with the oral history of native peoples and lends strong support for their claims.”

Detecting Sepsis

A patient is showing signs of whole-body inflammation. If it’s bacterial sepsis, the patient needs antibiotics, or he could die within hours. If it’s sterile inflammation, antibiotics could be counterproductive, opening the door to pathogens such as Clostridium difficile.

“We think we’ve got the makings of a diagnostic blood test that will allow clinicians to distinguish between these two types of inflammation,” says Purvesh Khatri, PhD, assistant professor of biomedical informatics research. Through a meta-analysis of 27 gene-expression data sets, he and Stanford colleagues found 11 genes that activate in response to sepsis, but not sterile inflammation. Postdoctoral scholar and surgical resident Timothy Sweeney, MD, PhD, is the lead author and Khatri is the senior author of the study, published in May in Science Translational Medicine.

Making rounds

THE HUMAN BRAIN IS HARD TO STUDY. IT IS, AFTER ALL, ENCASED IN THE SKULL. TECHNIQUES LIKE fMRI allow only broad visualization of brain activity. Post-mortem tissue can reveal brain structure, but not function.

Now, School of Medicine scientists have developed small spheres of human brain cells that mimic the architecture of the brain’s outer layer, the cerebral cortex. The researchers grew colonies of induced pluripotent stem cells from skin samples, then treated them in a special lab dish onto which the cells wouldn’t cling. The colonies folded themselves into spheres and some of the cells developed into neurons and astrocytes, support cells that maintain neural function.

Examining the spheres may shed light on human brain development and the molecular causes of neuropsychiatric conditions such as autism and schizophrenia. “We’ve been treating them just like we would slices of mouse brain, and trying to answer functional questions,” says Sergiu Pasca, MD, assistant professor of psychiatry and behavioral sciences and senior author of the study, which was published in July in Nature Methods.
Genes in common

JANE GOODALL’S OBSERVATIONS OF CHIMPS IN GOMBE Stream National Park revealed that they use tools, eat meat and make war. Now, School of Medicine scientists have discovered that some of the Tanzanian primates may resist the disease progression of SIV, the simian equivalent of HIV, for the same reason some humans do.

Humans who have a particular variant of HLA-B, a gene that codes for proteins that help the immune system recognize invaders, resist progression from HIV to AIDS. Some of the Gombe chimps have an analogous variant, a portion of which strongly resembles the human one — and infected chimps with the variant have lower fecal counts of SIV than infected chimps without.

The similarity of part of the chimp and human variants implies two things, says Peter Parham, PhD, professor of structural biology and of microbiology and immunology. First, hominids have been fighting off HIV-like viruses at least since the two species diverged some 5 million years ago. Second, because that particular section of the gene variant hasn’t changed much since then, it probably plays an important role in increased survival among those inheriting it.

Parham is the senior author of the study, published online in *PLOS Biology*. The work could lead to drugs or gene therapy to help people with HIV avoid progressing to AIDS.

LASER FOCUS

Stem cell treatments show promise for disorders such as Parkinson’s disease, which is characterized by defective nerve cells in specific brain regions. Results of stem cell transplants have been mixed, however, forcing researchers to guess what the cells are doing in the brain. • Until now. • Scientists led by Jin Hyung Lee, PhD, assistant professor of neurology, of neurosurgery and of bioengineering, have devised a method of monitoring neural stem cells transplanted into rats’ brains. Along with the cells, which contain a gene coding for a protein that induces electrical activity in response to blue laser light, the researchers implanted an optical fiber that could be connected to a light source. They then stimulated the cells with pulses of blue light. • Using fMRI and electrophysiology, the researchers were able to see that the cells matured into neurons and integrated into targeted circuits. The cells also fired when stimulated by the light, triggering electrical activity in downstream nerve circuits. • ”I’m hopeful that this monitoring approach could work for all kinds of stem-cell-based therapies,” says Lee, the senior author of the study, which was published in July in *NeuroImage*.

Proton-pump inhibitors, like Prilosec, account for 100 million prescriptions per year in the United States.

Change of heart

To reduce stomach acid, heartburn patients have a couple of options: H2 blockers like Pepcid or Zantac, or the stronger proton-pump inhibitors like Prilosec or Prevacid. The 20 million Americans who take PPIs may want to reconsider, say researchers, who have found a link between their use and the risk of a subsequent heart attack.

In a study published in June in *PLOS ONE*, lead author Nigam Shah, PhD, MBBS, assistant professor of biomedical informatics, and colleagues mined the electronic health records of 3 million people, comparing the frequency of subsequent heart attacks among PPI users with that of heartburn sufferers who were not using PPIs. They found a roughly 20 percent increase in the rate of heart attacks among PPI users. H2 blockers were not associated with increased cardiovascular risk.
“For in every adult there dwells the child that was, and in every child there lies the adult that will be.”

Author John Connolly wasn’t writing about human health when he penned this line, but it aptly describes a modern medical insight: Events that take place during our earliest years have far-reaching consequences for our health when we mature. Some of these consequences are obvious. A child diagnosed with Type 1 diabetes, for example, may grapple with eye or foot damage later in life. Others are becoming evident as survivors of once-fatal conditions are living further and further into adulthood. Children may conquer cancer only to face infertility, organ trouble and early osteoporosis as they grow older. And some outcomes illustrate the need to safeguard all aspects of kids’ health. A child who copes with chronic trauma — abuse, neglect, parental dysfunction — is more likely to have heart disease as an adult. • No matter the threat to children’s well-being, researchers are developing techniques to set them up for the healthiest possible adulthood. To see how they’re helping kids thrive, read on.
THE EFFECTS OF OUR EARLIEST EXPERIENCES
Hannah Blomdal stood in her darkened front yard, trying to surmount her fear. Her family’s suburban home looked calm, even bucolic, on the April evening. But the 17-year-old’s thoughts were agitated.

A FEW MONTHS EARLIER, the Redwood City, California, front yard had been the scene of an assault that sent Hannah to the hospital with a broken jaw, a skull fracture and bleeding on her brain. She had almost no memory of the attack, yet felt profoundly unsafe in the yard, especially at night. Her vigil alone there, plotted in advance with her psychotherapist at Lucile Packard Children’s Hospital Stanford, was part of a treatment program intended to help her brain exercise control over the danger signal. Subconscious tripwires such as Hannah’s fear of her front yard are a long-recognized feature of post-traumatic stress disorder, but we are just beginning to understand the damage inflicted by living with these internal alarms. That’s especially true when intense stress starts early in life. People traumatized in childhood, research now shows, can suffer decades of harm to their physical and mental health. “Some people think kids are protected by virtue of being kids. In fact, the opposite is true,” says Victor Carrion, MD, director of the Stanford Early Life Stress and Pediatric Anxiety

BY ERIN DIGITALE
ILLUSTRATION BY GÉRARD DUBOIS  PHOTOGRAPH BY MISHA GRAVENOR
Program and a leader in understanding the long-term effects of childhood trauma. Children are more likely to be harmed by traumatic experiences than adults, scientists have found, and the wounds do not heal without help. Instead, the effects of untreated trauma worsen with time, casting a long shadow over young people’s futures. Yet many pediatricians and psychiatrists aren’t aware that they should ask about children’s experiences of trauma. Absent such information, doctors can easily misdiagnose traumatized children with other psychiatric conditions, such as attention-deficit hyperactivity disorder, which has symptoms similar to PTSD but different origins and treatments.

However, there is good news in the form of a growing movement to get the word out about childhood trauma, coupled with effective new therapies for childhood PTSD. One such approach, a method Carrion developed called cue-centered treatment, was the technique that led Hannah Blomdal to stand in her front yard that spring evening, confronting her fears.

AWAKENING TO TRAUMA

WHEN CARRION WAS A pediatric psychiatry fellow at Stanford in the mid-1990s, he noticed a curious phenomenon. “Kids were coming to see me with little notes from their teachers that said, ‘This child has ADHD. Please place on Ritalin,’” Carrion says. Chuckling slightly, he recalls his half-facetious reaction to these missives: “Wow: A diagnosis has been made; there’s a treatment plan; there’s not much for me to do here.”

But after carefully obtaining life histories for several patients, he realized that although some had ADHD, many others had been traumatized by such experiences as abuse, neglect or witnessing violence in their homes or communities. Their reactions — a triad of self-protective behaviors that experts summarize as “freeze, fight or flee” — were being misinterpreted as ADHD’s signature inattentiveness, hyperactivity, aggression and poor cooperation.

“Teachers don’t realize that these out-of-control behaviors are manifestations of fear and helplessness,” says Alicia Lieberman, PhD, a professor of psychiatry at the University of California-San Francisco who studies trauma’s effects on young children. Like Carrion, she sees many untreated trauma sufferers labeled as problem kids.

Trauma during childhood is widespread. Experts estimate that about a third of U.S. children experience some form of trauma before they become adults, and of those, 3 to 15 percent of girls and 1 to 6 percent of boys develop full-fledged PTSD. But PTSD rates are much higher for kids who experience the worst traumas. More than a quarter of girls who are physically assaulted develop PTSD, as Hannah did. And researchers are also finding that childhood trauma can manifest in other ways, not just as full-blown PTSD.

The worrying realization that signs of childhood trauma were widely misunderstood led Carrion to wonder what trauma really did to his patients. Starting in the early 2000s, he launched a series of studies to track children’s levels of cortisol, a key stress hormone.

Chronic or unresolved trauma changes the body’s cortisol levels, he and other researchers found. The perturbations harm developing nerve cells, according to animal studies. In children, Carrion’s team linked the changes to impaired development and smaller structures in brain centers that form memories, make decisions, and register rewards and pleasure. These areas line up with trauma symptoms: memory, emotion regulation and decision-making are all hindered in people with PTSD.

At the same time that Carrion was studying cortisol and kids’ brains, the question of trauma’s lasting effects was also catching the attention of researchers studying adults. In the mid-1990s, scientists noticed that risk factors for chronic ailments such as heart disease were not randomly distributed in the population, instead concentrating in certain groups. Could childhood trauma help explain the discrepancy?

In 1998, the first of several scientific papers was published from the Adverse Childhood Experiences study, a survey of more than 17,000 adults enrolled in a large California HMO. The researchers tracked 10 types of childhood adversity: emotional, physical or sexual abuse; emotional or physical neglect; seeing domestic violence toward one’s mother; having a parent who was alcoholic or abused drugs, had a mental illness or was incarcerated; and parental separation or divorce. More than 60 percent of survey participants had experienced at least one of these forms of trauma and 12 percent had experienced four or more.

The ACE study connected adverse childhood experiences to a stunningly long list of physical illnesses in adults — ischemic heart disease, liver disease, obesity and sleep disturbances, among others — as well as many mental health issues, such as depression, illicit drug use and suicide attempts. Throughout the studies, researchers consistently found that adults who experienced more types of childhood trauma were at higher risk for each disease or bad outcome.

In 2011, Carrion and San Francisco pediatrician Nadine
A year after a brutal attack, Hannah Blomdal has returned to the softball field.
Burke Harris, MD, published a similar study that focused on Harris’ patients who lived in a violent, low-income San Francisco neighborhood. Risk for learning and behavior problems and for childhood obesity rose with increasing trauma exposure, they found.

The emerging evidence provides a startling contrast to the traditional narrative of why people with rough childhoods don’t do very well, the idea that bad role models and tough circumstances leave them without a map. The old story boils down to kids simply making bad choices. The new story is a lot more complicated: Children exposed to toxic levels of trauma have brains that aren’t well-equipped to handle fear or frustration; to remember things or exhibit the self-control needed for success in school; to avoid self-medicating their bad feelings with illicit drugs; in short, to make good choices. And even when they do make good choices as they mature, these long-traumatized adults are still at greater risk for physical illness than their peers who did not grow up with toxic levels of stress.

In 2012, the American Academy of Pediatrics issued a technical report that summarized much of this evidence and suggested that “many adult diseases should be viewed as developmental disorders that begin early in life.”

“We need to address trauma because it impacts health, period,” Carrion says. “Not just mental health; it impacts physical health as well.”

**BUILDING A NEW TREATMENT**

When Carrion began studying trauma, researchers had already scientifically validated more than a dozen trauma therapies, including several variations on play-based therapy for young children and cognitive behavioral therapy for older kids and teenagers. Medications sometimes help alleviate specific symptoms of trauma, but aren’t effective on their own, research has shown. But even with everything that was known about treatment, many young patients still weren’t helped sufficiently by it.

“I realized that what we call ‘PTSD kids’ is a really heterogeneous group,” Carrion says. The existing therapies worked best for children who had experienced a single horrible event in an otherwise stable life. “They could say, ‘Yes, I went through a fire; I have symptoms and when I talk about them, I get better,’” he says. “With other kids, when you ask about traumatic events, they look at you like you have two heads. For them, it’s always happening.”

Carrion and his colleagues began developing cue-centered treatment with these kids in mind. Though its techniques overlap with many other trauma therapies, two features set CCT apart. It can address all traumas a child has experienced, rather than asking him or her to pick a single bad event as the focus of treatment. Even more important, it gives kids insight into the “freeze, fight or flee” response. And in CCT, children work with a therapist to develop a tool kit of healthy coping skills that can replace the “problem” behaviors, such as using deep breathing and meditation techniques instead of running away from a setting that makes them panicky.

“Many kids see themselves as bad, a problem, crazy,” Carrion says. “We teach them that their response to trauma is something that was adaptive, and hence it was learned really well by their bodies as a good response. But when the response is maintained and triggered by reminders, it becomes maladaptive.”

“A lot of treatments start by asking, ‘What are the problem behaviors? Let’s fix them,’” says Hilit Kletter, PhD, a clinical instructor in psychiatry and behavioral sciences who worked with Carrion to develop CCT. “But we know that there’s a reason these maladaptive behaviors develop: It’s protective.”

Taking away a child’s sole defense without providing a healthy alternative can backfire, Kletter says. “They’re going to fight you to keep their one tool, so we don’t try to take it away; we offer alternatives.”

In the first randomized controlled trial of the treatment, published in 2013, Carrion and Kletter studied 65 children who had each experienced at least two and an average of five traumatic events. After 15 weekly counseling sessions, the kids had fewer PTSD symptoms. Their caregivers, who attended four of the sessions, also had less anxiety and depression. The scientists are now sharing the method: A manual for therapists describing how to conduct the treatment is in press. And although CCT was developed for children with ongoing adversity, it’s also proving useful for kids who experienced a single trauma.

Carrion is optimistic that the treatment will make a durable improvement in kids’ lives.

“Kids get it,” he says. “They can say, ‘That’s what’s happening to me,’ and become their own agents of change.”

**A SURPRISE ATTACK**

Unlike many traumatized children, Hannah Blomdal was not raised in a milieu of disaster. Before she was attacked in late 2014, she was an accomplished high school senior who was preparing to apply to a half-dozen top universities. She loved playing catcher and outfielder on her competitive softball team and adored her family’s four dogs. Her parents, Kim and John,
A LOT OF TREATMENTS START BY ASKING,
“What are the problem behaviors? Let’s fix them.”
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had made their suburban home a welcoming place not only for Hannah and her older sister, Meghan, but also for the girls’ friends. Two months earlier, Hannah’s best friend, Caitlin, had even moved in with the family, and the friends were so close that Hannah thought of her as another sister.

On Oct. 31, Hannah, Meghan, Caitlin and another friend, a young man who also lived with the Blomdal family, went to a parade in San Francisco for the Giants baseball team, which had won the World Series two days earlier. Later that evening, still dressed in their Giants gear, Hannah and Caitlin left the Blomdal house together to visit a local street known for its over-the-top Halloween celebrations.

After a few hours, the two girls came home. Hannah can recall almost none of what happened next.

Sometime later, the young man returned to the Blomdal house. He texted Hannah’s phone for help, saying he had lost his keys. But when she answered the front door, he attacked her. The Blomdals still aren’t sure if he used a weapon; Hannah remembers only her urge to scream.

When Hannah opened the front door, Kim and John were asleep in their room in the back of the house. At night, John uses a continuous positive airway pressure machine to help him breathe, and the noisy device at first masked Hannah’s screams. However, a neighbor heard her yelling, came outside to investigate and found Hannah in the street. The attacker assaulted the neighbor too. (The attacker later pled guilty to charges associated with both assaults and is now serving a prison term.)

Hannah’s injuries were severe. She was rushed in an ambulance to Lucile Packard Children’s Hospital Stanford for emergency surgery. Her surgeon, Gerald Grant, MD, used eight titanium plates and 64 surgical staples to put her skull back together.

Her jaw had been broken in two places, but Grant decided to let that heal on its own. He stitched up a large cut in her face.

After surgery, she spent a few days in a medically induced coma.

“It’s almost surreal, watching your daughter go through something like that,” Kim says. “You just put one foot in front of the other, hold your spine straight and walk through it; you can’t fall apart.”

When Hannah was discharged from the hospital on Nov. 5, her family was not sure what to do next.

“We were concerned for her physical and emotional health,” Kim says.

“And mental health, too,” adds John.

They are having this conversation sitting in their living room on a warm May afternoon, with Hannah in an armchair near both of them. Hannah looks healthy, and she is — she has just finished her spring season of softball, playing with as much enthusiasm as ever. The only visible remnant of the attack is a thin, white scar, perhaps 3 inches long, on her right cheek.

But John looks pained, as though his worry about his daughter’s recovery is still fresh. Using Hannah’s childhood nickname, he articulates what he was thinking when she first came home from the hospital: “How can we get Hootie as close back to where she was as possible?”

“I WAS KIND OF IN SHOCK,” says Hannah, recalling the weeks after the attack. Exhausted and struggling to recover from her injuries, she missed more than a month of school. In late November, she began cue-centered treatment with Kletter.

“I didn’t realize how out of tune with myself I was,” she says. “It was not until I started to sit down for an hour once a week, talking with Dr. Kletter, that I was able to have a full thought about it.”

“She was vacillating between being overwhelmed and feeling numb,” Kletter recalls. Because Hannah couldn’t remember the assault, it seemed unreal, like something that had happened to someone else. Although she lacked a conscious memory of the attack, certain things related to it sparked intense fears, such as standing in her family’s front yard. The fact that her attacker had lived with her family left

15-WEEK ROAD MAP

A 15-WEEK ROAD MAP

STANFORD MEDICINE FALL 2015

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her feeling especially vulnerable, wondering how she could ever again suss out others’ motives. And she wasn’t sure how to ask family and friends for help in handling her feelings, or even if she should.

“She’s very competent,” Kletter says. “She places a lot of expectation on herself that she should be able to do things, and not rely on others.”

Worst of all, she had lost her sense of momentum.

“When Dr. Kletter started to ask me what I thought about my priorities now, and where I could see myself going, that was a really big surprise,” Hannah says. “It wasn’t on my radar. I was taken aback.” Before the assault, she had never questioned her desire to go away to college; now “it was a really big question.” Maybe instead, she thought, she should just “stay at home and lay low.”

In this context, the road map Kletter described for 15 weeks of cue-centered treatment was a relief to the Blomdals, reassuring them that Hannah was expected to make clear, measurable progress.

The therapy began with a few sessions for Hannah and her parents about the trauma reaction, as well as an assessment of Hannah’s entire medical history. Kletter helped Hannah list her existing coping tools — meditation, exercise and listening to music — and figure out what new strategies she needed. They talked about how she could reframe her negative thoughts and how to manage panic before it got out of control.

Then, Kletter had Hannah tell the story of the attack. They also charted major events of Hannah’s life, rating each as positive, negative or neutral.

“The trauma, even though it felt like everything, was one point on the giant graph that was my life,” Hannah says. Seeing the chart helped her give more weight to positive events such as starting softball, which “sparked this big love, this passion I had for the game for so long.”

Next, Kletter and Hannah identified the triggers of Hannah’s strongest fears: being in her front yard, especially alone and at night; answering the front door; being home alone at night; Halloween; and scary movies. Between therapy sessions, Hannah practiced changing her response to each trigger, first imagining herself dealing with each scenario and then exposing herself to it in real life. As she did so, she rated her anxiety on a scale of 1 to 10. If it rose above a 3, she used one of her coping skills to handle it.

Her family helped. Her parents arranged for surprise visitors so that Hannah would have to answer the front door at unexpected times, and Meghan and Caitlin stood with her in the front yard as she worked up to the spring evening when she was first able to stand there alone. Gradually, she also figured out how to tell everyone what she needed: when she wanted to talk about the trauma; when she wanted them to stop tiptoeing and just treat her like her old self.

“Coming back to school, it felt like people weren’t looking at me; they were looking at my story,” she says. “They were not really making eye contact. It was, ‘She’s had a rough year.’” She tried to help her friends understand that she had not been eclipsed by one terrifying, random event: “I do appreciate your support, but I’m still here!” she says now.

“I could really see a shift in her energy,” says Kim. “There were glimpses of her confidence coming back.”

As Hannah’s treatment progressed, her confidence and momentum grew. She started hearing back from colleges to which she had reluctantly applied. She had been admitted to five schools, and decided to attend the University of California-Santa Cruz.

CARRION SEES stories like Hannah’s as a hopeful contrast to the directions that PTSD can take someone if it’s never addressed.

“Let me tell you, PTSD doesn’t disappear by itself,” he says. “It feeds on avoidance. If you don’t recognize it, or if a family tries to hide their big secret, or if a child doesn’t have words to describe what happened, it gets worse.

“And the pity is that it is so treatable. But if we don’t recognize our own traumas, they don’t just go away.”

Today, he’s focusing his work on two key areas: helping the health-care system recognize trauma, and boosting children’s resilience.

In the mid-2000s, Carrion was one of several experts who helped found a trauma-informed clinic in San Francisco’s impoverished Bayview neighborhood, where he had done much of his cortisol research. (San Francisco pediatrician Nadine Burke Harris, the San Francisco Child Abuse Prevention Council, the Tipping Point Community Foundation and then-district attorney Kamala Harris were also involved.) The Center for Youth Wellness, as the clinic is now called, has become a model for how to care for traumatized kids.

A key step in this caregiving, Carrion says, is eschew-
ing the traditional, singular focus on checklists of a child’s symptoms or “bad behaviors.”

Lieberman, at UCSF, puts it this way: “Doctors don’t ask, ‘What happened to this child?’ Instead they think, ‘What’s wrong with this child?’”

Parents, too, may not want to look at what’s really going on, especially if a parent is causing the problem. “Many times the parents don’t put two and two together; they have defenses against understanding the impact of the child’s experience on the child,” she says.

Government officials are turning resources toward child trauma. In February, Kamala Harris, now California’s attorney general, launched the Bureau of Children’s Justice to advocate for disadvantaged children, including those in foster care, in the juvenile justice system and living with a lot of trauma.

Nonprofit efforts are taking shape, too. Futures Without Violence, a nonprofit public benefit corporation that led work to pass the federal Violence Against Women Act in 1994, is now at the forefront of a movement to stop violence against children. Carrion has been involved in both efforts, and also serves on the California Mental Health Services Oversight and Accountability Commission. “To address childhood trauma, we need broad solutions that extend from neuroscience to advocacy and policy,” he says. “Our program’s activities span the whole spectrum.”

ONE OF THE MORE puzzling features of childhood trauma is its ability to elicit extremely varied reactions: Some survivors are badly debilitated, while others respond with great strength and creativity, a phenomenon known as post-traumatic growth.

“People who are highly traumatized have become extraordinarily creative and successful, but may also have episodes of deep depression and maladaptive relationships, and as parents they might be perpetuating the same problems with their children,” Lieberman says. “But because they’re so successful, nobody’s looking behind the façade.” She recalls a throwaway lecture comment by the late Norman Garmezy, a pioneer of resilience research: “But of course, when you talk to these very resilient people who have overcome great difficulty, they tell you how much they suffer when they are alone, when they’re not trying to show their successful persona to the world.”

Carrion’s next project aims to prevent that suffering. He’s leading a large study of teaching yoga and mindfulness meditation to children in schools throughout the Ravenswood City School District, which includes East Palo Alto and parts of Menlo Park. These schools, in a low-income community near Stanford, are full of students who live with the sorts of stresses he has studied. In the study, sponsored by the Sonima Foundation, his team is providing its curriculum to 3,400 students from kindergarten to eighth grade, and testing the program’s effects in a subset of third- and fifth-graders. They will assess the kids’ behavior and study their cortisol levels, sleep patterns and brain scans. The team hopes the training will give kids better ability to handle stressors that could derail them, ranging from everyday frustrations to full-blown trauma. So far, their pilot data look promising.

AT THE END of Hannah’s therapy, she retold the story of the Halloween night attack, giving Kletter a fresh take on the narrative she related at the start of her treatment. Together, they compared the two versions.

“It was easy to see that not only the way I was describing it, but also my emotions, thoughts and body feelings were less anxious than before,” Hannah says.

In the first telling, Hannah worried about what she should say. Would it be believable? Would it be enough?

In the retelling, Hannah took charge but also viewed her story from a wider lens, Kletter says. “She was coming to terms with, ‘This happened, but it’s not the defining point in my life; I have something to look forward to and focus on,’” she adds. “I was seeing a sense of hope in her.”

— Contact Erin Digitale at digitale@stanford.edu
In a dimly lit room, next to a supersonic jet engine test rig, three Stanford engineering graduate students sat around a whiskey bottle. All was quiet on this Friday evening in 2013 except for their lab’s visceral hum, a rumbling of fans, flames and gases rushing through jet-propulsion nozzles.

These three rocket-combustion experts — Christopher Strand, Victor Miller and Mitchell Spearrin — were talking about the future. In a few months they would have doctoral degrees, and then what? As boys, all three grew up away from big city lights, with a clear view of the stars in the night sky. And they dreamed about rockets and exploring space. Now that the space shuttle was grounded and its successor scrapped for being over budget, what would they do instead? Work at an aerospace company? Consult on military projects? It was Strand who initiated a series of brainstorming sessions that challenged them to think beyond outer space. “Somewhere between ideas on fixing San Francisco’s parking problem

**ROCKET MEN**

**ANALYZING THE BREATH OF CRITICALLY ILL CHILDREN AT WARP SPEED**

BY KRIS NEWBY
PHOTOGRAPHY BY MISHA GRAVENOR

MITCHELL SPEARRIN, VICTOR MILLER (SEATED) AND CHRISTOPHER STRAND DEVELOPED A QUICK, RELIABLE DEVICE TO MEASURE AMMONIA LEVELS.
and inventing a marijuana Breathalyzer, we decided to see if we could use our education and expertise in combustion science to analyze human breath for disease,” says Miller. “After all, the human body is essentially a biochemical engine. It consumes fuel and exhales waste gases. Maybe the three of them could engineer a disease Breathalyzer? It would be a gadget straight out of Star Trek — a quick, noninvasive way to detect everything from diabetes to cancers. Many have tried and failed to create such a device. But these guys are rocket men. They assume risks without fear. They achieve the impossible without breaking a sweat. They take giant leaps for mankind.

Sure, they didn’t know much about medicine, but they figured that with a little luck and a lot of hard work, they just might be able to do it. The first step was to find medical experts to help, so they contacted a group of pediatricians at Stanford’s medical school.

**SAVING ETHAN**

Five years ago, professor of pediatrics Gregory Enns, MD, was called into the neonatal intensive care unit at Lucile Packard Children’s Hospital Stanford to help a newborn in trouble. The child’s mother, Tiffany Nguyen, was a business software consultant and his father, Luan Pham, was a systems engineer. They were immigrants from South Vietnam, excited about starting a family in the United States. After 18 hours of labor, their baby boy was born. They called him Ethan, a biblical name that means “enduring strength” in Hebrew.

But the morning after his birth, Ethan cried continually. By noon, his blood sugar and temperature dropped. His body became limp. The attending pediatrician couldn’t figure out what was wrong, so two days after Ethan’s birth, the infant was moved from a San Jose community hospital to Lucile Packard Children’s Hospital Stanford. That was when Enns, a biochemical geneticist who diagnoses and treats metabolic diseases, was contacted.

When Enns first examined Ethan, the prognosis was grim. Ethan’s tiny heart was beating erratically and his blood sugar level was dangerously low. Enns didn’t think the child would survive the night. But he put this possibility out of his mind and did his best. Enns, with his reassuring smile, quirkly cartoon ties and clear blue eyes, is also a professional optimist. First, the cardiac team was called in to help stabilize Ethan’s heart. Then Enns tried to figure out why Ethan’s blood sugar was so low. He suspected that Ethan had a genetic defect of the metabolic system. This could result in a buildup in the bloodstream of ammonia, a chemical that is normally detoxified by the liver. The blood test for this condition, called hyperammonemia, is slow and unreliable. Its analysis takes about an hour. By the time Ethan’s blood test came back, the level of toxic ammonia was almost 10 times higher than normal. Even if Ethan survived the next few days, he would always be at risk of another ammonia surge that could cause serious brain damage if not treated promptly.

Ammonia is a chemical byproduct released when the human body turns one type of fuel — specifically, digested protein molecules — into energy. The body eliminates this toxic waste by converting it in the liver to nontoxic urea, then sending it through the kidneys so it can be eliminated in urine. If anything goes wrong in this chain of organs and biochemical processes, ammonia builds up.

At this point there wasn’t time to do an in-depth genetic analysis to figure out what was wrong, so Enns expedited a biochemical blood test that revealed Ethan’s body was unable to digest long-chain fatty acids, a major component of breast milk and its precursor, colostrum. Because of this, Ethan’s body lacked enough energy to fuel his vital organs.

So Enns fed Ethan intravenously with a solution of high-calorie sugar and medium-chain fats. Then he administered a drug to remove the excess ammonia circulating in his bloodstream. Against the odds, this strategy saved Ethan’s life.

“Ethan was the sickest child in the intensive care unit I’ve ever seen turn around,” Enns says.

Once Ethan was out of danger, Enns sat down with the parents to talk about the realities of caring for a child with a metabolic disorder. It requires constant vigilance. They have to protect Ethan’s metabolism from stress, especially viruses. And they have to be alert to signs of lethargy and confusion — indications of high ammonia levels. If they suspect an excess of ammonia, a life-or-death drill will be initiated. Rush to the hospital. Watch a phlebotomist poke the child with needles
for the blood tests. Wait an hour for test results. If the result is high, hospital staff will administer ammonia-grabbing drugs and intravenous fluids, retest the blood and repeat as needed. Delayed treatment could lead to permanent brain damage or even death.

Enns has a superhuman ability to connect with patients and families in these difficult situations. Most of the children he works with have extremely rare diseases, for which research is limited and treatment plans are based on comfort care, guesswork or some combination. He is able to talk with a 10-year-old with severe developmental disabilities at exactly the right level, then turn to offer advice to parents on health insurance issues, never lapsing into technical doctor-speak.

When asked how he protects himself from the emotional stress associated with these conversations, Enns points to his prematurely silver hair and says, “I don’t.”

This was the dilemma for Enns: He could save these newborns, but then what?

Hope came out of the blue two years later, when he received a call from David Stevenson, MD, senior associate dean for maternal and child health at Stanford. Stevenson told him he knew of three Stanford rocket engineers with a novel idea for analyzing human breath, and they were looking for a medical condition to try it on. Would Enns collaborate with them? Enns immediately thought about patients like Ethan, and he jumped at the chance to help.

“Maybe these engineers could succeed where many others had failed,” says Enns. “I thought, after all, they’re rocket scientists.”

MISSION CONTROL

The idea for the disease breath analyzer was born in Stanford’s High Temperature Gas Dynamics Laboratory. This lab, tucked into an unobtrusive, sandstone-and-tile building behind Stanford’s Main Quad, has served as the launch pad for almost 100 combustion engineers, all of whom earned their doctorates under the mentorship of mechanical engineering professor Ronald Hanson, PhD.

In 2013, two of Hanson’s students — Christopher Strand and Victor Miller — sat at adjacent desks overlooking a “Rockets of the World” poster. They were both finishing dissertations on supersonic combustion ramjets, called scramjets for short. Strand was working on better ways to measure engine gas mixtures using lasers. Miller was developing gas-flow visualization techniques using lasers and high-speed cameras.

Scramjet technology, conceptualized in the 1950s, still presents researchers with extreme technical challenges. These engines use atmospheric oxygen to burn their fuel rather than having to carry liquid oxygen along for the ride. This allows scramjet-equipped craft to fly at speeds of more than five times the speed of sound. Theoretically, aircraft equipped with these engines could fly anywhere on Earth within 120 minutes. Scramjet space planes could carry greater payloads and operate more efficiently.

Strand, now 30, tall and lean with British-schoolboy wavy brown hair, has always wanted to be an astronaut. He was
raised on a small farm in rural Alberta, Canada, the son of a single mother who worked as a bookkeeper. Strand didn’t apply to college during high school. But when he accompanied his girlfriend (now wife) to her first day of classes at the University of Alberta, he realized he’d made a horrible mistake. "All of a sudden I knew that I belonged at a university," Strand says. So that week, through a fortuitous connection, he met with the dean of engineering and talked his way into the school’s engineering-physics program.

Miller, 28, with mischievous eyes and the energy level of someone who just downed a triple espresso, is a fix-anything guy with a penchant for testing boundaries. He’s also a drummer in a ‘90s cover band called Cloning Dolly. He grew up in Watertown, Wisconsin, a small town an hour east of Madison. His father was an ex-Marine-turned-engineer and his mother was a travel agent. As a boy, he was obsessed with airplanes. He graduated from Cornell University, summa cum laude, in mechanical and aerospace engineering.

Miller’s worldview had been influenced by a year in Stanford’s Accel Innovation Scholars program, which gives 12 PhD students access to entrepreneurial leaders in Silicon Valley. This program encourages bright engineering scholars to explore ways to apply their knowledge to some of society’s biggest challenges. In other words, Miller had absorbed the culture of Stanford entrepreneurship.

Strand also felt the allure of inventing a Silicon Valley “new new thing,” he says. “I think Vic and I empowered each other to pursue breath sensing. There is a certain confidence that comes with having a partner.”

When the team first began looking into the breath analyzer idea, a search of scientific literature revealed that breath testing with the human nose has been used in medicine since ancient times. The rotten-apple smell of acetone is a sign of diabetes. The smell of putrid socks is associated with kidney problems. A fishy smell is indicative of liver disease. Though these nose-based diagnostic skills are still used by some clinicians today, many researchers have recognized the opportunity to develop a medical device that could transform this art into a science.

The late Nobel laureate and Stanford chemistry professor Linus Pauling was one of the pioneers of modern breath testing. In the 1970s, he used a gas chromatograph to detect several hundred volatile organic compounds in breath, providing the first evidence that it is a more complex mixture of gases than anyone had imagined. Since then, more than 3,000 compounds have been detected. And though the signatures of ingested chemicals, like alcohol, may be easy to measure, it’s much more difficult to detect disease biomarkers, unique combinations of small molecules that may be present only in trace quantities in human breath.

The engineers figured that the technology they used in rocket testing, laser absorption spectroscopy, would be sensitive enough to make measurements of trace compounds in the breath. For detecting gases in combustion flows, the technology works like this: A laser beam at a specific frequency is fired across a stream of burning gases, and a sensor on the other side of the beam measures the quantity of light that is transmitted through the gases. From this information, gas properties like temperature, velocity and the chemical com-
position of the exhaust gas mixture can be identified almost instantaneously. Just as engineers can use these data to tell if an engine is operating efficiently, they could tell if a human “engine” is operating in a healthy range.

To analyze the gases in human breath, Miller and Strand realized they’d need a laser that emits light in the mid-infrared frequency range. They also needed someone experienced in this range, and luckily, there was just such an expert on the other side of the rocket lab: Mitchell Spearrin.

**ALL SYSTEMS GO**

Spearrin’s life trajectory was set when he watched a rocket from Cape Canaveral soar over his home near Bryceville, Florida, population 3,000. “I wanted to be an astronaut,” says Spearrin, 31, who is married with two daughters and looks like someone who might be cast as a square-jawed hero in a Hollywood blockbuster.

Although the U.S. space program was nearby, this career goal seemed light years away from his small, rural town. As a kid, he focused on sports and became the captain of his high school football and baseball teams, a natural leader. He also was good at math and graduated as the straight-A valedictorian of his senior class.

Encouraged by his parents, an elevator mechanic and a stay-at-home mom, Spearrin was determined to be the first in his family to attend college. He also hoped to play sports at the collegiate level, and it was through football that he found himself unexpectedly recruited by Harvard late in his senior year. In a matter of weeks he went from never having considered an Ivy League school to committing to Harvard’s football program and, in turn, an education he could not have fathomed. It eventually led him to Stanford’s mechanical engineering doctoral program.

During his time at Harvard, Stanford and a stint at aerospace manufacturer Pratt & Whitney, Spearrin fell in love with rocketry. “These machines represent a certain pinnacle of engineering: rockets control a convolution of physical extremes with a precision driven by intolerance for human error,” he says.

Spearrin, who at one point was voted by his Harvard football teammates as “most likely to start a business,” liked the idea of the breath analyzer, so he joined the effort. And at that point, they had a team in place. Strand knew about lasers. Miller knew about gas handling and photonics hardware. Spearrin knew about rapid analysis of gases using mid-infrared lasers. And Enns agreed to be their medical research mentor.

They started off the project with two roundtable discussions that included Enns, Stevenson and several other pediatricians. (Stevenson had worked on breath analysis of bilirubin, a chemical that can signal jaundice in newborns, early in his career.) They discussed the most urgent clinical needs for newborns, and ammonia screening rose to the top. A second priority would be to detect acetone, a diabetes marker, in newborns.

The graduate students then wrote a three-page proposal for their breath ammonia analyzer and submitted it for a pilot grant from Spectrum, a Stanford program that funds researchers with bold ideas for addressing important health-care problems. (Primary funding for these grants comes from the Spectrum Clinical and Translational Science Award from the National Institutes of Health.) They were awarded $49,000 to launch the project and teamed up with an industry mentor, Darlene Solomon, PhD, senior vice president and chief technology officer of Agilent Technologies. Then the countdown began. They had a year to get a prototype working.

“I thought it was a simple, elegant solution — though at the time, it seemed as if was too simple to actually work, given the small quantities of ammonia they were trying to measure within the complexity of human breath” says Solomon.

The project got off to a slow start. The funds were delayed, and all three engineers had rocket science “day jobs” to work around.

They began with a schematic on how their device works. A person blows into a tube and breath gases are collected in a pressure-regulated cylinder that directs a controlled gas stream across a mid-infrared laser beam. When the beam hits ammonia, the molecules absorb specific wavelengths of light. A photodetector measures the amount of light that passes through the ammonia, then custom software calculates quantities of ammonia and plots it on an easy-to-read graph on a laptop computer. The device also measures carbon dioxide as a way of telling the software that one breath cycle is complete and another one is beginning.
The first prototype used a clear quartz tube for the gas cylinder, which Miller purchased for $50 on eBay from an equipment salvager in Austin, Texas. The breathing tube was attached to one end of the cylinder. Flow meters, pumps and valves were attached to the other end, all scavenged from the rocket lab. These would direct the gas stream across the laser beam. Optical mirrors directed the laser beam onto the photodetector. Initially, the prototype was built on an 8- by 4-foot table with a Rube Goldberg array of gas-handling tubes, pumps and pressure gauges sprawled above and below. The team began to make its first measurements of breath ammonia, and during the first trial runs realized why no one had ever successfully developed an ammonia breath analyzer.

“Ammonia is a nightmare to work with,” says Spearrin. Because the molecules are highly soluble in water and have an unstable electrical charge, they tend to stick to everything, including the inside of the human mouth and the walls of plastic tubing. So they switched to nonstick Teflon tubing. Temperature fluctuations distorted ammonia measurements, so an on-board heater and insulation had to be added to the device.

Finally, after six months of tweaking, the team brought its second-generation prototype into a quarterly grant-review meeting. The prototype was packed inside a custom box, which was placed on a wheeled cart. Beneath were a data acquisition system and various measurement instruments, all of which would be miniaturized into a more compact format in a commercial product.

A volunteer from the meeting blew into the tube, and a graph of the levels of ammonia and carbon dioxide in that given breath appeared on the computer screen.

Enns’ first impression of the rapid, easy-to-use device was “jaw-dropping amazement.”

WE HAVE LIFTOFF

With the help of Enns, the engineers received Institutional Review Board permission to test their ammonia breath analyzer on human subjects, specifically two 16-year-old boys admitted to the hospital for hyperammonemia. These teens were representative of their target patient population — they were cognitively and physically impaired from ammonia surges. One used a wheelchair. Both spoke slowly, in broken sentences.

It brought home the importance of why the team was working on the breath analyzer project.

Their plan was to have the teens blow into the device’s breathing tube after each of their blood draws over the two or three days it would take to normalize their ammonia levels. But they soon realized that it was difficult to explain to the teens how hard to blow.

Finally, Strand figured out a strategy that worked. He gave the boy the tube and said, “Pretend that this is your elephant nose and make a sound like an elephant.”

This insight prompted the team to redesign the software to provide visual feedback that showed patients when they were blowing hard enough. They also started designing a passive, under-nose breathing tube that could be used without active blowing, which will be necessary for some patients but requires more sensitive detection.

Patient testing also refined their thinking on the technological advantage their device brings to the field. The major weakness of the ammonia blood test is that by the time the results are received by a treating physician, it is hour-old information that may not represent the true ammonia levels of a patient. The breath analyzer enables super-fast, repeatable testing so ammonia levels can be verified and treatment can begin immediately.

“Babies breathe so fast that it’s hard to get an accurate ammonia reading using a device with a slow response time,” says Spearrin. “What our device is really good at is rapidly measuring intra-breath dynamics, showing how the chemical composition of a breath changes over time.”

In just a year, the team had gone from a rough idea on paper to a working prototype, patient-tested. This is warp speed in the medical device world. They are also preparing articles for publication describing the underlying spectroscopy, the device and, ultimately, their clinical studies.

Spearrin didn’t realize how hard this project was supposed to be until he called a respected expert on hyperammonemia for advice. Before Spearrin could ask his questions, the expert said, “You’ve chosen a horribly challenging project because ammonia is the most difficult molecule to measure and newborns are the most difficult patient population to work with.”

Spearrin replied, “But we’ve already built a working prototype and we’ve tested it on two patients.”

In the fall of 2015, the team is planning a second, larger patient trial that will involve younger children. There’s a good chance Ethan will be in that trial. Since they finished their first prototype, they’ve received grants from the NIH’s Small Business Technology Transfer program and the Wallace H. Coulter Foundation. The Stanford Office of Technology and Licensing has filed a provisional patent, and the team has formed a company, Lumina Labs. The company, funded by the NIH small business grant, has established a research consortium with Enns and Stanford.
“What impressed me about this development team is that they really listened to all the advisers’ technical concerns, methodically addressing each one. And they did so while still getting a prototype into testing amazingly quickly,” says Solomon.

WAITING TO EXHALE

Five years after his birth, Ethan Pham, with chubby cheeks and bear-cub ears, looks and acts like a typical kindergartener. His mother — a halo of dark hair framing her ivory face — plays with him as he sits in his hospital bed, happily singing with cartoon farm animals on TV. On the bed tray is a sheet of paper where he has practiced writing his name with crayons.

Ethan is recovering from a surgical procedure to insert a tube through his chest into an artery of his heart. This permanent IV port will make it easier for the care team to quickly administer ammonia-grabbing drugs when needed. In the past, a nurse would have done this by inserting a syringe into an arm blood vessel, but with so many pokes over the years, it became hard to find an undamaged, free-flowing vein. He’s also under observation for high, unexplained fluctuations of ammonia.

It takes a dedicated team to keep Ethan alive. His family, schoolteachers and medical practitioners are continually on the lookout for signs of high ammonia levels. Episodes can happen at any time. Each incident means a 30-minute drive to the critical care unit, where staff members stand ready to draw blood. Ethan’s medical team — his pediatrician, Rebecca Fazilat, MD, at Sutter Health San Jose; Enns; and the hospital staff at Stanford Children’s Health — is on call 24/7.

Many times the ammonia blood tests, which can be done only at the hospital, are wrong or ambiguous. If the test is positive, it typically takes a day or two in the hospital to normalize the ammonia levels, with repeated blood tests every few hours. Sometimes the family is halfway home when a nurse calls them back to redo a test. Ethan has spent about half of his kindergarten year in the hospital.

Ethan’s teachers have been trained to accommodate his condition. His work areas must be extra clean and sick kids need to be kept away. His diet is carefully monitored — no birthday cake, since he can't digest it. Ethan doesn’t have the muscle strength to climb on the playground equipment, so he often sits on the side, playing with his plastic farm animals or trying to kiss Catherine, a girl in his class he really likes.

Nguyen and Pham, like most parents who have children with metabolic defects, are perpetually fatigued. When Ethan is in the hospital, Nguyen stays by his side and her husband joins her after work. They often eat dinner at the hospital cafeteria. Nguyen’s parents and sister live close by, and they help out when they can. For Nguyen, it’s a full-time job keeping Ethan from slipping into an ammonia-induced coma.

What keeps them going is their faith (Nguyen is a Catholic and Pham is a Buddhist) and the hope that someone, maybe even the rocket men, will find a better way to test ammonia levels in children with metabolic diseases at the hospital and at home. This would allow Ethan, with his enduring strength, and his family to live a more normal life.

BLUE-SKY THINKING

It’s worth looking at the breath analyzer project and asking, what can fuel more of these big ideas in medicine?

Spearrin recently summed up what motivated his team: “For us, it’s not that ammonia sensing is the perfect challenge. It’s that the breath analysis field is underdeveloped. We’re leaders in this particular gas-analysis technology, and there are clinical researchers here at Stanford really open to collaborating with us. It gives us a chance to make a significant contribution through cross-disciplinary efforts.”

What worked was to empower an ambitious team of young engineers to look at an old medical problem with fresh eyes. They were given starter funds to try out their big ideas without fear of failure. There was institutional buy-in, making it acceptable for people outside of the medical system to observe, ask questions and change the way things have been done in the past. And they were given access to mentors who could inspire them, help remove bureaucratic roadblocks and keep them from making big mistakes.

Strand adds, “Being in a clinic and working with kids gave me a unique sense of purpose that I haven’t felt in my research before. I’ve had the good fortune of getting to be part of a lot of exciting and challenging research, but never where the need is so tangible, urgent and, most certainly, so personal. It makes a difference if this problem is solved today instead of tomorrow.”

Of course, anyone familiar with medical device development would be quick to add that there’s a tremendous amount of work to be done before the ammonia breath analyzer is widely available. There need to be more prototypes. Clinical trials. Independent validations. But one thing we all can probably agree on is this: Medicine needs more rocket scientists.

— Contact Kris Newby at krisn@stanford.edu
CHILDHOOD  
The road ahead  

WHEN I GROW UP  
HELPING CHRONICALLY ILL KIDS MAKE THE JUMP TO ADULT CARE

Yana Vaks, MD, was about to begin a year of postdoctoral research at Stanford, studying the health of children with chronic medical conditions after they become too old for pediatric care, when she saw the worst of what can happen.

“There was an 18-year-old who came to the hospital in crisis,” she says. “He had a liver transplant when he was 8, but when he turned 18 he wanted to start a new life and decided he was done with all that extra health consciousness his transplant meant.” The patient had stopped taking the drugs necessary to keep his body from rejecting the transplant and neglected to see his doctor regularly. By the time Vaks saw him, his transplanted liver had begun to fail, starting a catastrophic process that affects all body systems. “It was a shocking case,” she says. • The teenager died the next day. • “His mother said the biggest change had been that because he was 18, she was no longer in control of what medications he took and what he didn’t take,” Vaks says. “Unless there’s a plan for letting go, it can be disastrous.” • Right now, there is no standard road map for doctors and hospitals to help children with chronic illness transition from pediatric to adult care. And the need

BY SARA WYKES  
ILLUSTRATION BY DANIEL HOROWITZ
for a plan is increasing. More and more children are living beyond the bounds of pediatric care, simply because medicine has improved. Many of the specialists who have treated them recognize that their transition from childhood to adulthood is risky: Young adults may be grown in body, but they aren’t always ready psychologically or socially to take full responsibility for consistently following complicated medical routines and practicing lifestyle restrictions. “You can’t just expect patients leaving pediatric care to be an adult patient when they haven’t developed any skills,” says Lynn Kjelson, MPH, a kidney transplant coordinator at Stanford Children’s Health. This recognition is translating into a call to action from medicine’s leaders for specialized training, certification and research into best practices — including a recent project at Stanford’s Clinical Excellence Research Center.

“A problem like this has suffered from a lack of ownership,” says Dennis Lund, MD, chief medical officer at Stanford Children’s Health. “Is it the pediatrician’s problem if there’s a 25-year-old having difficulty finding the right care or that of the adult patient’s doctor with no expertise in pediatric diseases? When you reach adulthood, you don’t want to go to a children’s hospital and sit in an exam room with Pocahontas on the wall. It’s become a national issue.”

A handful of care providers, including several teams at Stanford Children’s Health, have formal transition programs in place. But most do not. A 2011 joint report in Pediatrics from the American Academy of Pediatrics, the American Academy of Family Physicians and the American College of Physicians called for a systematic approach to the problem. The recent project at Stanford’s Clinical Excellence Research Center makes specific recommendations for pediatricians, pediatric specialists, patients and parents to prepare for the jump to adult care.

Some medical conditions, including cystic fibrosis, diabetes, rheumatoid arthritis, movement disorders and transplantation, require lifelong, daily maintenance and ongoing specialized medical treatment. Others, like congenital heart disease, require lifelong but not daily care, and physicians with knowledge particular to the condition — including in adulthood. Doctors have recently begun to call for special attention to transition care for survivors of childhood cancer, who must learn to live with the long-term effects of the treatment that saved their lives, including higher risk of infertility; early-onset bone weakness; chronic problems with heart, liver, kidney and hormone function; impairments in sexual function; and development of other cancers. Doctors are also beginning to think about how to help patients with mental illnesses that emerge in childhood and change with age.

The Clinical Excellence Research Center, established in 2010 to study, design and demonstrate ways to improve health care while reducing costs, identified transition care as a good candidate for the changes it hopes to effect with its work. “We’re trying to figure out how to do the right thing and have it be affordable,” says Dana Steidtmann, PhD, a co-leader of CERC’s two-year project on transition care. Young adults with chronic illness may soon constitute 10 percent of the U.S. population ages 15 to 25, she says, compared with 1 percent before advances in treatment.

To understand the problem, the CERC team did a thorough review of scientific articles; interviewed adolescent patients, their parents and clinicians throughout the United States; reviewed advances in information and communications technology; and visited several hospitals around the country to observe successful transition programs for all major chronic diseases before constructing its recommendations.

Sue Fernandes, LPD, a clinical associate professor of pediatric cardiology and the program director of the Adult Congenital Heart Program at Stanford Children’s Health and Stanford Health Care, became one of the team’s advisers for the project. Previously, Fernandes had conducted research that identified gaps in the transition process. Among her findings: More than half of parents reported their child’s pediatric cardiology team had never mentioned the need for lifelong care.

Then there are the adolescents themselves. Being responsible for making medical appointments, renewing medications, negotiating insurance coverage and learning how to take an active part in health-care decisions — these tasks may become second nature with age, but many young adults don’t want or know how to do them, especially at the intense and ongoing level certain chronic illnesses demand. “Young adults do not want to have to think about their health every day,” says Steidtmann. “They have a strong desire to feel normal.”
Their parents, meanwhile, aren’t often prepared to change doctors or cede control. “As the parent of a child with a serious chronic illness, you are a warrior who has gone through years of learning the ins and outs of your child’s condition,” says Elizabeth Malcolm, MD, director of implementation and evaluation at CERC. “By the time your child graduates from high school, you think you have it all wired and it’s incredibly scary to think about your child moving to a new doctor or to a new place.”

The CERC team’s recommendations emphasize that pediatricians and pediatric specialty teams must be guides in this process: equipping patients and parents with information so they can anticipate the transition, coaching patients to develop the confidence and skills needed to manage their health, and locating and being available to specialists and primary care physicians who will need certain medical knowledge to care for their patients as adults.

The recommendations provide a structure to organize transition care for any condition. They suggest using a checklist to tailor plans; identifying a transition team leader to oversee the process and a transition guide to ensure each step is carried out; and using health coaches, telemedicine and other technologies like cellphones with health-tracking apps to make the transition steps as feasible as possible for patients, families and doctors. The team calculated that if these transition programs were widely implanted, they could avoid preventable disability, hospital visits and other medical expenses totaling $200 million a year.

**PIONEERING PROGRAMS**

**STANFORD CHILDREN’S HEALTH** has pioneered transition programs for patients, parents and pediatric physicians. As soon as children go on the kidney-transplant list, for example, post-transplant coordinators begin working with them and their parents. “We start our teaching early so it will be part of their life,” says Kjelson, the physician assistant who coordinates the team. “We do that to establish rapport and to build familiarity with the transition process.” After a post-transplant patient turns 12, the clinical team begins split appointments, seeing the patient and parents separately. “We do that to allow patients to develop those self-care and advocacy skills, Stanford Children’s before the patient is accompanied to the adult medical team.”

The transition plan also includes a 10-step checklist that covers matters such as transferring medical history and ensuring patients and parents understand how insurance coverage can change in adulthood. The final step: a goodbye visit at Stanford Children’s before the patient is accompanied to his or her first adult appointment by someone from the pediatric team.

Linden Moore was born with a congenital heart defect and has had six surgeries. Her first was 11 days after her birth. Her last was quite recent — after her 18th birthday — so she had to sign her own consent form for the first time. It was a symbolic moment. “My parents and I were going, ‘Oh, my God!’ she says. “It was kind of surreal — that I’ve grown up with this and now it’s in my hands.”

Linden’s latest care transition is more complicated than moving from Stanford Children’s Health to Stanford Health Care: She began college in Oregon this fall. “You have a twinge of worry,” says her mother, Mary Moore. “No mom ages out of that. And you have to make sure that your child understands, as they take the reins, that they have certain rights. You have to teach them how to find information, to tap into resources and to ask questions.”

“In health matters, most parents do everything and children do what they’re told,” says Christy Sillman, the nurse coordinator for Stanford’s Adult Congenital Heart Program. “The child isn’t expected to advocate.” To help young adults develop those self-care and advocacy skills, Stanford Children’s Health has organized an Adolescent and Young Adult Heart Clinic. There, the care team understands patients’ concerns — even those that might seem small to others. “We know that life expectancy for most adult congenital heart survivors is fairly normal, but the life experience is not nor-
mal,” Sillman says. “While all their friends are going out for pizza, they’re restricted to a low-sodium diet.”

At Stanford’s Bass Center for Childhood Cancer and Blood Diseases, co-director Sheri Spunt, MD, oversees a Health After Therapy Program designed to ease patients’ transition from cancer treatment to survivorship. Her team equips its patients with a notebook containing their entire health history and a treatment summary, as well as personally tailored care guidelines for adult survivors of childhood cancer. The guidelines come from the Children’s Oncology Group, an international organization of 9,000 experts in childhood and adolescent cancer and a National Cancer Institute clinical trials research group. “Many health-care practitioners are unaware that these guidelines exist,” says Spunt, the Endowed Professor of Pediatric Cancer. “With about one in 650 young adults who’ve become cancer survivors, doctors need to be educated about this. People think the cure is the victory, but cure is not sufficient; you need cure with long-term care that supports quality of life.”

PILOTING THE PLAN

AFTER ANALYZING THE STATE of transition care, the CERC team has launched pilot programs to test its recommendations. A pilot at Stanford Children’s Health focuses on the effectiveness of a health coach in strengthening the health management skills of chronically ill young adults, specially crafted to the feelings that can drive neglect of medical needs. “We coach from a different perspective than a medical team would,” says health coach Jacqueline Nguyen, a former CERC research assistant. “We say, ‘We know it’s hard for you to be responsible for your care, but let’s think about all the reasons why it might be important for you. Instead of saying, ‘If you don’t take your meds. … ,’ we say, ‘If you take your meds, you’re going to feel better and do better in school and go away to college.’”

The CERC team’s recommendations will be piloted on a larger scale in the diabetes clinics of Intermountain Healthcare, a Salt Lake City-based system of 22 hospitals. The region has a high and increasing rate of diabetes, says Carolyn Reynolds, the registered nurse who directs Intermountain’s Pediatric Specialties Clinical Program. The 250 patients in the pediatric diabetes program will be given an experienced care-management clinician, a transition guide and a health coach to support them as they take over their own care. Intermountain’s multi-hospital system could eventually serve as a testing ground for the ability of the Stanford plan to be adapted to various medical specialties. “Everyone we’ve talked with has thought this program is needed,” Reynolds says. “When it was presented to our Parent Advisory Council, they said, ‘Let’s do it today.’”

WHEN TRANSITION WORKS

JON MICHAIEL, 23, was born with kidney failure and received his first kidney transplant when he was 11. As he approached his 18th birthday, he needed a second one — which meant he stayed with his Stanford Children’s Health doctors for another three years. As comfortable as he felt with them, he wanted to be more independent. “I didn’t have the autonomy to make decisions and my parents were with me in appointments, which wasn’t very cool for someone my age,” he says. “I was ready to go to the adult side, but I was apprehensive about meeting a whole new care team.”

Once he made the transfer, he felt the difference immediately. “The pediatric team is very hawk-eyed with its patients,” he says. “On the adult side, there’s no social worker or liaison to remind you if you’re late on your meds. There is a lot more you have to think about.”

A transplant “is a solution, not a fix,” Michaiel says. “It’s something you need to deal with and manage, just like people manage jobs responsibly. You do have to grow up a lot faster than most people do.” When the rigors of maintaining his health become challenging, he reminds himself of the dedication of his family and his pediatric team. “It took a lot to get me here, so I don’t want to mess up,” he says. “I am one of the lucky ones.”

— Contact Sara Wykes at swykes@stanfordhealthcare.org
In his endeavor to advance democracies around the world, Carter has observed 100 elections in 38 countries. Renowned for projects in global health, the center counts among its greatest successes the eradication of the tropical disease Guinea worm. Collaborations between the center, ministries of health and local communities have cut the disease’s incidence from 3.5 million cases in 1986 to just 126 today. According to the center, Guinea worm is set to become the second human disease in history, after smallpox, to be eradicated.

Carter’s post-presidency has been declared by many historians as one of the most successful of any U.S. president. So you might think that after all of his achievements, which include receiving the 2002 Nobel Peace Prize and authoring 27 books, Carter would have been thinking of retiring. Well, you would be wrong. At 91 he is dedicating the remainder of his life to promoting equality for women and girls. His recent book, A Call to Action: Women, Religion, Violence, and Power, is a manifesto detailing the discrimination that women and girls face worldwide. Well-known as a Christian and a Bible class teacher for more than 70 years, Carter specifically challenges those who use religious texts to deny women’s equality. He writes, “Women and girls have been discriminated against too long in a twisted interpretation of the word of God. … The world’s discrimination and violence against women is the most serious, pervasive and ignored violation of human rights.”

In this issue of Stanford Medicine, Carter talked with executive editor Paul Costello about the plight of women and girls around the globe. Since their conversation early this summer, Carter announced he is being treated for cancer, and in a subsequent email, Carter wrote to Costello, he is “at ease, and grateful.”

Paul Costello: Why, at 91 years old, are you making equality for women and girls the highest priority for the rest of your life?

Jimmy Carter: The human rights violation of women and girls is the most serious human rights problem on Earth. At the Carter Center, we’ve had programs in 80 countries. The human rights issue was brought to a highly personal level when we saw the horrible and surprising abuse of women and girls all around the world, including in the United States.

Costello: By the end of 2014, nearly 60 million people were refugees. Half were children. That’s 30 million children essentially homeless.

Carter: One of the parts in my book describes a particular plight of women and children who are living in refugee camps. Quite of-
ten, the housing there is just tents with no doors to keep predators out. They just come through the flap and make life miserable for the women, who are there quite often in a defenseless way.

Most often their husbands are away and not able to protect them. That’s a special problem for women and children, not only being displaced but also without the normal protections of a house. It’s a problem for everybody who is a refugee, but I would say that, in a wartime environment, the women and children suffer most.

COSTELLO: You’ve said women and girls have been discriminated against through the misinterpretation of religious texts. What are some of the ways this plays out?

CARTER: In the early Christian church, until the third century after Christ, women played a very strong and dynamic role. In the 16th chapter of Romans, Paul named about 25 people who played leading roles in the early church, and almost half were women who were apostles, bishops and priests. That changed as men became dominant in the Catholic Church, which set the basis for everybody else.

When someone who has an inclination to abuse a woman, say an oppressive husband, sees that in the eyes of the church, women are inferior to God, then they assume that women are inferior to all men.

COSTELLO: You write that 14 million girls are married each year before they reach the age of 18. What are the ramifications of this?

CARTER: Let me give you an experience I had recently in Nepal. Young girls there are often taken from home and sent to India, either to work in brothels or sold into marriage. My wife, Rosalynn, and I met with 18 rescued girls the last time I was in Nepal. Toward the end of our long conversation, I asked them, would you rather be sold into sexual slavery in a brothel, or sold into an unwanted marriage? Unanimously, they said that forced marriage was much worse just because they went through it. They think it’s the proper thing to do. In Egypt, girls under 15 have a substantially lower percentage of sexual mutilation than older girls. The publicity and changing international awareness is having some beneficial impact.

COSTELLO: What are some of the sensitivities that Westerners need to be especially cautious about when they’re trying to tackle these cultural customs and practices?

CARTER: I would say that a holier-than-thou attitude is probably the worst. You can’t go into a culture like I just described in Egypt or in the rest of Africa or Asia and say, ‘We are perfect in our country, and you need to reform the way you treat women.’

In the United States, we have a horrible problem with human trafficking. Also, in two of our most revered American institutions — our universities and our military — the abuse of women is horrendous. About one out of five girls who enters an American university is sexually assaulted before she graduates. The U.S. military has pointed out that 26,000 sexual assaults were perpetrated in the military the year before last. The State Department reported last year that 60,000 people are basically living in some form of human bondage in America. These are the kind of things of which we’re very guilty in our country, so we can’t preach to others.

COSTELLO: If you could do one thing that would forcefully change the status of women and girls around the world, what would that be?

CARTER: One of the main things we could do is get the United Nations Security Council to pass strong legislation, a condemnation of elements that harm girls and women. The U.N. Committee on the Elimination of Discrimination Against Women is a very wonderful expression of international commitment to do away with discrimination against women. The United States has failed to ratify that.

COSTELLO: What motivates you now? What drives your passion?

CARTER: I’ve always been committed to human rights, and I see the abuse of women and girls as the worst example of that on Earth. It is not being addressed adequately.

I have the influence of a former president, and I find the work of the Carter Center to be very challenging, unpredictable, adventurous and also gratifying. I enjoy being active, traveling and promoting what I consider to be the correction of violations of the Universal Declaration of Human Rights. SM

WEB EXTRA
Hear the conversation at http://stan.md/1NDQahY

This interview was condensed and edited by Paul Costello.
Carolyn Walworth, 17, often reaches a breaking point around 11 p.m., when she collapses in tears. For 10 minutes or so, she just sits at her desk and cries, overwhelmed by unrelenting school demands. She is desperately tired and longs for sleep. But she knows she must move through it, because more assignments in physics, calculus or French await her. She finally crawls into bed around midnight or 12:30 a.m. • The next morning, she fights to stay awake in her first-period U.S. history class, which begins at 8:15. She is unable to focus on what’s being taught, and her mind drifts. “You feel tired and exhausted, but you think you just need to get through the day so you can go home and sleep,” says the Palo Alto, California, teen. But that night, she will have to try to catch up on what she missed in class. And the cycle begins again. “It’s an insane system. … The whole essence of learning is lost,” she says.

WALWORTH IS AMONG A GENERATION OF TEENS GROWING UP CHRONICALLY SLEEP-DEPRIVED. According to a 2006 National Sleep Foundation poll, the organization’s most recent survey of teen sleep, more than 87 percent of high school students in the United States get far less than the recommended eight to 10 hours, and the amount of time they sleep is decreasing — a serious threat to their health, safety and academic success. Sleep deprivation increases the likelihood teens will suffer myriad negative consequences, including an inability to concentrate, poor grades, drowsy driving incidents, anxiety, depression, thoughts of suicide and even suicide attempts. It’s a problem that knows no economic boundaries. • While studies show that both adults and teens in industrialized nations are becoming more sleep-deprived, the problem is most acute among teens, says Nanci Yuan, MD, director of the Stanford Children’s Health Sleep Center. In a detailed 2014 report, the American Academy of Pediatrics calls the problem of tired teens a public health epidemic.

By Ruthann Richter

ILLUSTRATION BY CHRISTOPHER SILAS NEAL
SOCIAL AND SCHOOL PRESSURES PROMPT MANY STRESSED TEENS TO FORSAKE SLEEP
“I think high school is the real danger spot in terms of sleep deprivation,” says William Dement, MD, PhD, founder of the Stanford Sleep Disorders Clinic, the first of its kind in the world. “It’s a huge problem. What it means is that nobody performs at the level they could perform,” whether it’s in school, on the roadways, on the sports field or in terms of physical and emotional health.

Social and cultural factors as well as the advent of technology all have collided with the biology of the adolescent to prevent teens from getting enough rest. Since the early '90s, it’s been established that teens have a biologic tendency to go to sleep later — as much as two hours later — than their younger counterparts.

Yet when they enter their high school years, they find themselves at schools that typically start the day at a relatively early hour. So their time for sleep is compressed, and many are jolted out of bed before they are physically or mentally ready. In the process, they not only lose precious hours of rest, but their natural rhythm is disrupted, as they are being robbed of the dream-rich, rapid-eye-movement stage of sleep, some of the deepest, most productive sleep time, says pediatric sleep specialist Rafael Pelayo, MD, with the Stanford Sleep Disorders Clinic.

“When teens wake up earlier, it cuts off their dreams,” says Pelayo, a clinical professor of psychiatry and behavioral sciences. “We’re not giving them a chance to dream.”

UNDERSTANDING TEEN SLEEP

ON A SUNNY JUNE AFTERNOON, Dement maneuvered his golf cart, nicknamed the Sleep and Dreams Shuttle, through the Stanford University campus to Jerry House, a sprawling, Mediterranean-style dormitory where he and his colleagues conducted some of the early, seminal work on sleep, including teen sleep.

Beginning in 1975, the researchers recruited a few dozen local youngsters between the ages of 10 and 12 who were willing to participate in a unique sleep camp. During the day, the young volunteers would play volleyball in the backyard, which faces a now-barren Lake Lagunita, all the while sporting a nest of electrodes on their heads.

At night, they dozed in a dorm while researchers in a nearby room monitored their brain waves on 6-foot electroencephalogram machines, old-fashioned polygraphs that spit out wave patterns of their sleep.

One of Dement’s colleagues at the time was Mary Carskadon, PhD, then a graduate student at Stanford. They studied the youngsters over the course of several summers, observing their sleep habits as they entered puberty and beyond.

Dement and Carskadon had expected to find that as the participants grew older, they would need less sleep. But to their surprise, the youngsters’ sleep needs remained the same throughout the teen years — roughly nine hours. “We thought, ‘Oh, wow, this is interesting,’” says Carskadon, now a professor of psychiatry and human behavior at Brown University and a nationally recognized expert on teen sleep.

Moreover, the researchers made a number of other key observations that would plant the seed for what is now accepted dogma in the sleep field. For one, they noticed that when older adolescents were restricted to just five hours of sleep a night, they would become progressively sleepier during the course of the week. The loss was cumulative, accounting for what is now commonly known as sleep debt.

“The concept of sleep debt had yet to be developed,” says Dement, the Lowell W. and Josephine Q. Berry Professor and a professor of psychiatry and behavioral sciences. It’s since become the basis for his ongoing campaign against drowsy driving among adults and teens. “That’s why you have these terrible accidents on the road. People carry a large sleep debt, which they don’t understand and cannot evaluate.”

The researchers also noticed that as the kids got older, they were naturally inclined to go to bed later. By the early 1990s, Carskadon established what has become a widely recognized phenomenon — that teens experience a so-called sleep-phase delay. Their circadian rhythm — their internal biological clock — shifts to a later time, making it more difficult for them to fall asleep before 11 p.m.

Teens are also biologically disposed to a later sleep time because of a shift in the system that governs the natural sleep-wake cycle. Among older teens, the push to fall asleep builds more slowly during the day, signaling them to be more alert in the evening.

“It’s as if the brain is giving them permission, or making it easier, to stay awake longer,” Carskadon says. “So you add that to the phase delay, and it’s hard to fight against it.”

PRESSURES NOT TO SLEEP

AFTER AN EVENING WITH FOUR OR FIVE HOURS of homework, Walworth turns to her cellphone for relief. She texts or talks to friends and surfs the Web. “It’s nice to stay up and talk to your friends or watch a funny YouTube video,” she says. “There are plenty of online distractions.”
While teens are biologically programmed to stay up late, many social and cultural forces further limit their time for sleep. For one, the pressure on teens to succeed is intense, and they must compete with a growing number of peers for college slots that have largely remained constant. In high-achieving communities like Palo Alto, that translates into students who are overwhelmed by additional homework for Advanced Placement classes, outside activities such as sports or social service projects, and in some cases, part-time jobs, as well as peer, parental and community pressures to excel.

At the same time, today’s teens are maturing in an era of ubiquitous electronic media, and they are fervent participants. Some 92 percent of U.S. teens have smartphones, and 24 percent report being online “constantly,” according to a 2015 report by the Pew Research Center. Teens have access to multiple electronic devices they use simultaneously, often at night. Some 72 percent bring cellphones into their bedrooms and use them when they are trying to go to sleep, and 28 percent leave their phones on while sleeping, only to be awakened at night by texts, calls or emails, according to a 2011 National Sleep Foundation poll on electronic use. In addition, some 64 percent used electronic music devices, 60 percent used laptops and 23 percent played video games in the hour before they went to sleep. More than half reported texting in the hour before they went to sleep, and these media fans were less likely to report getting a good night's sleep and to feel refreshed in the morning. They were also more likely to drive when drowsy, the poll found.

The problem of sleep-phase delay is exacerbated when teens are exposed late at night to lit screens, which send a message via the retina to the portion of the brain that controls the body's circadian clock: It's not nighttime yet. Yuan, a clinical associate professor of pediatrics, says she routinely sees young patients in her clinic who fall asleep at night with cellphones in hand.

“With academic demands and extracurricular activities, the kids are going nonstop until they fall asleep exhausted at night. There is not an emphasis on the importance of sleep, as there is with nutrition and exercise,” she says. “They say they are tired, but they don’t realize they are actually sleep-deprived. And if you ask kids to remove an activity, they would rather not. They would rather give up sleep than an activity.”

Adolescents are also entering a period in which they are striving for autonomy and want to make their own decisions, including when to go to sleep. But studies suggest adolescents do better in terms of mood and fatigue levels if parents set the bedtime — and choose a time that is realistic for the child’s needs. According to a 2010 study published in the journal Sleep, children are more likely to be depressed and to entertain thoughts of suicide if a parent sets a late bedtime of midnight or beyond.

In families where parents set the time for sleep, the teens’ happier, better-rested state “may be a sign of an organized family life, not simply a matter of bedtime,” Carskadon says. “On the other hand, the growing child and growing teens still benefit from someone who will help set the structure for their lives. And they aren’t good at making good decisions.”

According to the national sleep poll, by the time U.S. students reach their senior year in high school, they are sleeping an average of 6.9 hours a night, down from an average of 8.4 hours in the sixth grade. The poll included teens from across the country from diverse ethnic backgrounds.

American teens aren’t the worst off when it comes to sleep, however; South Korean adolescents have that distinction, sleeping on average 4.9 hours a night, according to a 2012 study in Sleep by South Korean researchers. These Asian teens routinely begin school between 7 and 8:30 a.m., and most sign up for additional evening classes that may keep them up as late as midnight. South Korean adolescents also have relatively high suicide rates (10.7 per 100,000 a year), and the researchers speculate that chronic sleep deprivation is a contributor to this disturbing trend.

By contrast, Australian teens are among those who do particularly well when it comes to sleep time, averaging about nine hours a night, possibly because schools there usually start later.

Regardless of where they live, most teens follow a pattern of sleeping less during the week and sleeping in on the weekend to compensate. But many accumulate such a backlog of sleep debt they don’t sufficiently recover on the weekend and still wake up fatigued when Monday comes around.
Moreover, the shifting sleep patterns on the weekend — late nights with friends, followed by late mornings in bed — are out of sync with their weekday rhythm. Carskadon refers to this as “social jet lag.”

“Every day we teach our internal circadian timing system what time it is, is it day or night, and if that message is substantially different every day, then the clock isn’t able to set things appropriately in motion. In the last few years, we have learned there is a master clock in the brain, but there are other clocks in other organs, like liver or kidneys or lungs, so the master clock is the coxswain, trying to get everybody to work together to improve efficiency and health. So if the coxswain is changing the pace, all the crew become disorganized and don’t function well. … So nothing goes as it’s supposed to.”

This disrupted rhythm, as well as the shortage of sleep, can have far-reaching effects on adolescent health and well-being, she says.

“It certainly plays into learning and memory. It plays into appetite and metabolism and weight gain. It plays into mood and emotion, which are already heightened at that age. It also plays into risk behaviors — taking risks while driving, taking risks with substances, taking risks maybe with sexual activity. So the more we look outside, the more we’re learning about the core role that sleep plays,” Carskadon says.

Many studies show students who sleep less suffer academically, as chronic sleep loss impairs the ability to remember, concentrate, think abstractly and solve problems. In one of many studies on sleep and academic performance, Carskadon and her colleagues surveyed 3,000 high school students and found that those with higher grades reported sleeping more, going to bed earlier on school nights and sleeping in less on weekends than students who had lower grades.

Sleep is believed to reinforce learning and memory, with studies showing that people perform better on mental tasks when they are well-rested.

“We hypothesize that when teens sleep, the brain is going through processes of consolidation — learning of experiences or making memories,” Yuan says. “It’s like your brain is filtering itself — consolidating the important things and filtering out those unimportant things.” When the brain is deprived of that opportunity, cognitive function suffers, along with the capacity to learn.

“It impacts academic performance. It’s harder to take tests and answer questions if you are sleep-deprived,” she says.

That’s why cramming, at the expense of sleep, is counterproductive, says Pelayo, who advises students: “Don’t lose sleep to study” or you’ll lose out in the end.

THE PANIC ATTACK

CHLOE MAUVAIS, 16, HIT HER BREAKING POINT at the end of a very challenging sophomore year when she reached “the depths of frustration and anxiety.” After months of late nights spent studying to keep up with academic demands, she suffered a panic attack one evening at home.

“I sat in the living room in our house on the ground, crying and having horrible breathing problems. It was so scary. I think it was from the accumulated stress, the fear over my grades, the lack of sleep and the crushing sense of responsibility. High school is a very hard place to be,” says the senior at Menlo-Atherton High School.

Where she once had good sleep habits, she had drifted into an unhealthy pattern of staying up late, sometimes until 3 a.m., researching and writing papers for her AP European History class and prepping for tests.

“I have difficulty remembering events of that year, and I think it’s because I didn’t get enough sleep. The lack of sleep rendered me emotionally useless. I couldn’t address the stress because I had no coherent thoughts. I couldn’t step back and have perspective. … You could probably talk to any teen and find they reach their breaking point. You’ve pushed yourself so much and not slept enough and you just lose it.”

The experience was a kind of wake-up call, as she recognized the need to return to a more balanced life and a better sleep pattern, she says.

But for some teens, this toxic mix of sleep deprivation, stress and anxiety, together with other external pressures, can tip their thinking toward dire solutions.

Research has shown that sleep problems among adolescents are a major risk factor for suicidal thoughts and death by suicide, which ranks as the third-leading cause of fatalities among 15- to 24-year-olds. And this link between sleep and suicidal thoughts remains strong, independent of whether the teen is depressed or has drug and alcohol issues, according to some studies.
I n h i s S e n i o r Y e a r in high school, one of James Underwood’s friends left a Friday night party around 12:30 a.m. and nodded off at the wheel in a remote stretch of rural Arkansas. Exhausted after a long week, including early-morning commutes to school, he veered off the road and struck a tree about a mile from home.

“It was kind of a shock to everyone,” says Underwood, now a sophomore at Stanford University.

Fortunately, his friend suffered no major injuries, but Underwood realized the consequences could have been catastrophic. The experience motivated him to volunteer in Stanford’s Sleep Ambassadors program, designed to teach high school students about the importance of sleep — and the dangers that lurk when they don’t.

T h r o u g h the p r o g r a m, which has won awards from the California School Boards Association and the National Sleep Foundation, Stanford students and faculty in the undergraduate-level Sleep and Dreams class reach out to every freshman at the nearby Menlo-Atherton High School to give them a primer on the value of sleep. The college students also pair up with juniors from the high school, who continue to spread the gospel among their peers as part of an ongoing educational campaign.

It’s a unique program among high schools nationwide, where sleep is rarely part of the curriculum, says Stanford sleep expert William Dement, MD, PhD, who helped start the project.

“It’s still true that sleep is not addressed in the educational system,” he says. “It’s terrible. All over the country it’s a huge problem.”

In the winter of 2016, the program will be expanded to Palo Alto’s two high schools — Gunn High School and Palo Alto High School — where student stress has been an issue of concern, says Rafael Pelayo, MD, a pediatric sleep specialist at the Stanford Sleep Disorders Clinic and one of the professors in the program. Pelayo also has made presentations to parents, teachers and students at the schools to encourage healthy sleep habits among the teens.

T h e p r o g r a m w a s s e a r c h e a d e d in 2006 by a passionate group of parents who had connections to Dement and to Mark Rosekind, PhD, now the administrator of the National Highway Traffic Safety Administration and an expert on human fatigue.

Dement says he had served as an expert witness in far too many tragic car accidents and was primarily concerned with drowsy driving among the teens. “I had learned that drowsy driving was the No. 1 cause of traffic fatalities. High school is when most students are learning to drive,” he says.

Some two-thirds of all sleepiness-related crashes involve adolescents and young adults, who don’t always perceive that they are fatigued and may be prone to risk-taking, studies show.

“...A lot of people have the mindset, ‘I’ll be fine. I can make myself stay awake. I’m invincible.’ But that’s not really true,” Underwood says. “If you’re not surrounded by a stimulus, you can crash very suddenly. … So it can be incredibly problematic.”

In addition to lessons on drowsy driving, the program teaches students about the basics of teen sleep and the many ways in which sleep deprivation can affect their lives, affecting memory, attention, learning and mood, among other things.

“We try to give them what they need to know going into high school at a time when sleep deprivation is so common,” says Marleya Mohler, a Stanford sophomore and one of the teaching assistants for this year’s class. “Sleep is seen as a kind of joke and not a serious topic. … There’s definitely a stigma that people who sleep a lot aren’t having fun. Pulling an all-nighter is like a badge of honor, a diehard commitment.”

Around the time the program was introduced at Menlo-Atherton, a group of parents pressured the school board to change the bell schedule as part of the campaign to improve students’ sleep habits. The high school’s 7:45 a.m. start time was pushed back to 8:45 a.m., with classes starting twice a week at 9:30 a.m. That gives students a midweek respite to catch up on sleep, rather than rely on the weekend to recover from their accumulated sleep debt, says outgoing principal Matthew Zito.

Zito thinks those changes and other innovations, such as a ban on AP summer classes and a homework-free winter break, have helped improve student well-being.

“Student behavior is greatly improved. The number of disciplinary actions of a serious nature is dramatically reduced. This isn’t all related to student sleep. The campus has improved its facilities and made other changes. But I think sleep is a factor in having a healthier academic and socio-emotional climate on the campus,” he says.
ONE OF STANFORD’S NEWEST FACULTY MEMBERS,
GARY DARMSTADT, MD, KNOWS IT’S POSSIBLE TO SAVE THE LIVES OF HUNDREDS OF THOUSANDS OF newborn babies worldwide without building hospitals or dispensing pricey drugs. In a groundbreaking endeavor, his team worked with communities to slash newborn mortality by 54 percent in less than two years in a large, impoverished area in northern India called Shivgarh. Their strategy was simple, in principle: embrace the local culture, seek to understand its newborn-care practices, and partner with the community to translate evidence-based recommendations into meaningful communications — metaphors, songs — that could change behavior. Even more strikingly, their method wasn’t really medical. The team’s most technical recommendation was to sterilize sickles used to snip umbilical cords. But despite its success, the spillover from the Shivgarh study — conducted in 2004 and 2005 — has been difficult to discern. Nearly 3 million newborns still die each year, according to a 2014 Lancet study, and many global health experts remain focused on more highly technical interventions. Yet Darmstadt and his colleagues know that many of these babies could be saved using the team’s community-based tactics. They’re continually refining their methods, looking to improve the principles they developed a decade ago in rural Shivgarh. They published their guiding framework in 2010 and additional details this summer in Seminars in Perinatology. Thanks to their community approach, they do more than just save babies; they also empower women and those in lower social classes, and

BY BECKY BACH
improve maternal health. These principles have been adopted as part of Indian health policy, and they inform current World Health Organization recommendations on newborn care.

**A TRADITIONAL BEGINNING**

The Shivgarh project started small, just two men, one truck and a bit of funding. Darmstadt had teamed up with Vishwa-jeet Kumar, a public health researcher he met while both were at the Johns Hopkins Bloomberg School of Public Health. Kumar, who has an Indian medical degree known as an MBBS, is charismatic and effusive, while Darmstadt is reflective and empathetic. They had both been pondering a 1999 study that showed a 62 percent reduction in newborn mortality in a community in western India due almost entirely to interventions provided in homes, not in a medical setting. They wondered whether these findings were replicable. And what were the key ingredients that led to such a significant reduction in mortality? Could mothers, families and communities be empowered to save their newborn babies without medical intervention?

To them, Shivgarh was the obvious choice for their public health experiment, which was funded by the United States Agency for International Development (better known as USAID) and by Save the Children US via a grant from the Bill & Melinda Gates Foundation. The population was poor and rural, with female literacy rates under 40 percent, an 8 percent neonatal mortality rate and deeply ingrained beliefs in the omnipotence of spirits and gods. Shivgarh’s loose coalition of villages, with about 100,000 residents, encapsulated the health-care challenges posed by communities across southeast Asia. “It was the epicenter of public health challenges,” Darmstadt says. “If you could crack a problem here, you had really achieved something and it’s likely what you had learned could have some impact elsewhere.”

The duo first arrived in 2003, venturing into villages surrounded by rice and mango fields, where the winter fog penetrated with a chilling dampness. With a small team of local social scien-
Villagers knew they had to

STICK THEIR UTENSILS IN FLAMES AND CLEAN THEIR HANDS BEFORE MAKING YOGURT OR PANEER, OR ELSE THE CURD WOULD SPOIL. THE TEAM EXPLAINED THAT BABIES NEEDED THE SAME TREATMENT, OR ELSE THEY TOO WOULD ‘SPOIL.’

If the baby lives through its first week, mother and baby leave the saur and rejoin the community, where the baby is welcomed with a ceremony, given a name and dressed in clean clothes.

IT TAKES A VILLAGE

To most Westerners and physicians, these practices seem nonsensical, even shocking: They leave their babies in cow dung?! But for Darmstadt and Kumar, the locals were “donors of knowledge,” equal partners rather than research subjects irrationally attached to harmful practices.

Team members had to vigilantly check their biases. “We had to continually remind ourselves to ‘Go out there and empty your mind,’” Darmstadt says. “It was really important to suspend that sense that you know something about what you’re observing until you’ve spent quite some time there.”

By asking probing, yet respectful questions, they learned that most of the practices surrounding childbirth in Shivgarh were developed to cleanse the baby from the perceived pollution of the womb and to protect babies from evil spirits, the supernatural forces thought by the largely Hindu population to be responsible for a variety of hardships. That insight made the villagers’ seemingly counterproductive behavior appear quite logical.

“Many of the things they do are driven by the same fears,” Kumar says. “We look for the cause of the cause and the cause of the cause of the cause, until we get just a handful of things, and that’s where we hit.”

The team set to work developing interventions that capitalized on the community’s belief system and could help its newborns. A breakthrough came when Darmstadt, Kumar and their team realized the practices that could lead to infections were also linked to hypothermia. Cold itself was dangerous, yet the community, though well-versed in other temperature-based concepts, lacked an understanding of, and a word for, hypothermia. Infection, which posed greater risk to the newborn, was even more elusive.

“The concept of germ theory per se was meaningless to them,” Darmstadt says. “The way we ended up providing the...
same concept was through an analogy.”

Villagers knew they had to stick their utensils in flames and clean their hands before making yogurt or paneer, or else the curd would spoil, Darmstadt says. Similarly, the team explained that babies needed the same treatment, or else they too would “spoil.”

“We tried to identify the path of least resistance to behavior change,” Darmstadt says. Their messages had to be believable; otherwise, they wouldn’t be adopted by community members and could even be seen as unnecessarily risky.

To address risks from both infection and hypothermia, the team worked with the community, which coined the term thandā bukhār; which translates as “cold fever.” The team made a list of desired interventions that addressed the risk factors for newborn deaths that they were seeing, and then translated each into a culturally tailored message. These messages typically were framed as metaphors that connected new practices for newborns with familiar concepts drawn from village life. For example, to encourage mothers to dry the baby after birth, they said: “When you come out after a dip in the pond, if you just wipe your face, won’t you feel cold? Similarly, if you just wipe the face of the baby, the baby will feel cold and develop thandā bukhār.” They enlisted the help of community leaders; for example, after learning of the importance of breast milk, local priests agreed to advise mothers to begin breastfeeding immediately after birth. They also trained local health-care workers, as well as the domin and nauns, on the benefits of using clean equipment and how to recognize common danger signs of illness, giving them new skills and increasing their value to the community.

Pregnant women and mothers-in-law, who play a critical role in perpetuating the community’s childbirth traditions, were shown how to provide skin-to-skin care, a simple practice that involves placing the bare-skinned baby on the caregiver’s skin, providing love, warmth and access to nourishment. The practice produces immediate, tangible benefits: It improves babies’ color and temperature, and reduces crying and startle responses. The villagers interpreted these signs as the absence of evil spirits, reinforcing their willingness to embrace the change.

With the groundwork set, the team was ready to launch a formal study. Kumar and Darmstadt divided the community into three groups with between 5,200 and 8,000 households each. One group was the control — they continued birthing and caring for children as they had for centuries. One group received a package of interventions the team called “essential newborn care,” which included home visits from trained workers and community meetings sharing the new behavior-change messages the team had developed with members of the community. Some of those meetings also featured folk songs, specially written by community members to communicate practices they had learned to protect the babies. The third group received the same set of “essential newborn care” practices, but they also were provided a liquid crystal hypothermia indicator called a ThermoSpot. The team tracked each of the group’s pregnancies (about 4,000) over a 16-month period (January 2004 to May 2005).

The results, published in the Lancet in 2008, were definitive: The interventions reduced newborn mortality by 54 percent. The benefit of ThermoSpot was minimal — it was the changed practices such as skin-to-skin care and breastfeeding, rather than technology, that saved babies’ lives.

Zulfiqar Bhutta, PhD, MBBS, co-director of the Centre for Global Child Health at The Hospital for Sick Children in Toronto and one of Darmstadt’s frequent collaborators, called the work pioneering.

“At the time, there was not a lot of evidence this could work at scale,” Bhutta says. “This study also proved the point that you could make a huge impact on mortality.”

GOING GLOBAL

Now, nearly a decade later, the Shivgarh study is recognized for making significant advances in newborn care. Its principles informed a 2009 World Health Organization/UNICEF strategy document on the importance of home visits for newborns. The state of Uttar Pradesh, which counts Shivgarh’s residents among its population of about 200 million, drew on the study to develop guidelines for its health-care workers, and some of the principles even made their way into India’s national health policy. Darmstadt finds it particularly rewarding to hear the term thandā bukhār while traveling in the region — evidence the dangers of hypothermia for newborns have infiltrated the health-care community and become common knowledge in villages. Darmstadt hopes other researchers will be inspired by their approach, but he recognizes one size does not fit all; each public health endeavor presents particular challenges that require customized adaptations.

In Shivgarh itself, the infant mortality rate continues to drop and the newborn care practices Darmstadt and Kumar

CONTINUES ON PAGE 55
One sultry evening in late July, Suresh Bojja entered the swirling vortex of traffic in this burgeoning south Indian metropolis. The roads here are a microcosm of life in India, as man and vehicle feverishly compete for every inch of space in a desperate effort to move forward, or even just survive. • Bojja had just finished his shift as a transit supervisor for Amazon and climbed on his motorbike to navigate through the cars, trucks, buses, rickshaws, motorbikes, bicycles and pedestrians that choke the streets, the air filled with exhaust and the relentless...
cry of beeping horns. Suddenly, three people on a single motorcycle headed directly into his path, sending him flying into the air and onto the ground. In a fit of road rage, fueled by alcohol, the trio then pummeled him in the head, face and stomach, leaving him for dead on the pavement.

In the not-too-distant past, Bojja likely would have met his end there, as medical aid was virtually nonexistent on India’s roadways, the site of 10 percent of the world’s traffic deaths.

But today India has created what some once considered unimaginable: the world’s largest ambulance service and the first of its kind in the developing world, which reports saving more than 1.4 million lives in its first 10 years. The system, known as GVK EMRI (Emergency Management and Research Institute), is a centralized 911-type network in which members of the public can call a single number to summon a team of trained professionals to provide aid en route to the hospital for a wide range of medical emergencies.

In minutes, an ambulance crew rescued Bojja and brought him to Gandhi Hospital, the nearest government facility, where he lay in a coma for 2 1/2 days. Two weeks later, he stands in his brother’s tidy two-room apartment, his left eye visibly damaged enough to frighten away his two children. But he is upright and his mind
clear as he quietly thanks those who came to his aid.

“The ambulance reached me in time,” he says in halting English. “If not, I might have lost my life from my injuries. My life is a present — they saved my life. I am very thanks for that.”

On Aug. 15 — India’s Independence Day — hundreds of GVK EMRI officials as well as 10 faculty and staff members from the Stanford University School of Medicine celebrated the 10th anniversary of the system at its headquarters, festooned for the occasion in orange, yellow and green marigolds. Begun with just 14 ambulances in one state, GVK EMRI has expanded to a fleet of nearly 10,000 ambulances, manned by some 20,000 medical professionals who ply the roads in cities and rural villages to provide access to emergency care to 750 million people — three-quarters of India’s population. It continues to expand, with G.V.K. Reddy, EMRI’s chair and managing director, announcing at the celebration that he had just inked an agreement with Sri Lanka to bring the service there, likely by the end of the year.

The public-private nonprofit provides its services free of charge, and 85 to 90 percent of its beneficiaries are the poorest of the poor.

“It’s amazing to see what’s been accomplished in a very short period of time. It’s very inspirational to me,” Lloyd Minor, MD, dean of the School of Medicine, told the crowd at the festivities. “Today’s celebrations are an opportunity to affirm our collective commitment. We look forward to working with the leadership on more programs in the future.”

Stanford Medicine physicians have been instrumental in helping bring the system to life, training the country’s corps of paramedics and designing India’s first emergency protocols — a 108-page tome of emergency care that is carried on every ambulance. Stanford physician-scientists also conduct research on emergency trends that continuously guides improvements in patient care.

“It’s hard to fathom what this system has done in 10 years,” says S.V. Mahadevan, MD, interim chair of Stanford’s Department of Emergency Medicine and founder of Stanford Emergency Medicine International, which brings emergency medicine programs to countries as far-flung as Mongolia, Cambodia and Myanmar, and provides medical expertise to GVK EMRI. “It could be regarded as one of the most important advances in global medicine in the world today.”

A GRAND VISION

IN THE SPRING OF 2005, MAHADEVAN RECEIVED AN UNEXPECTED VISIT IN HIS PALO ALTO, California, office from an Indian businessman, Venkat Changavalli, who had flown halfway around the globe for the sole purpose of meeting with him. Changavalli described a grand plan to set up a countrywide ambulance system in India and broached the idea of a partnership with Stanford. Mahadevan was deeply skeptical, as something like this had never been accomplished before in a developing country, particularly one as large, diverse and bureaucratic as India. After the meeting, he drove Changavalli to San Francisco International Airport without signing on, assuming he’d never see him again.

“I remember thinking, ‘This guy wants to start an ambulance service that covers all of India. It will never happen,’” recalls Mahadevan, an associate professor of emergency medicine. To his great surprise, he received an invitation a week later to the launch of the new service on Aug. 15, 2005 — a service they hoped to improve and expand with Stanford’s expertise. He decided to travel to India for the ceremonies and came away impressed with how the founders had adapted India’s legendary call-center technology for use in the medical arena, he says.

The system was launched by a passionate group of business and medical professionals who wanted to rescue the countless people dying from treatable injuries and illness simply because they had no way to get to a hospital in time, Ramana Rao, MD, DPH, director of EMRI’s emergency medicine learning center and research, says in an interview in his office.

“Most of the time they were waiting for the graces of God,” Rao says. “Some people made attempts by rickshaws, bullock cars, taxis, three-wheelers and sometimes bicycles. People would put a cot on their shoulders and carry someone down from the top of the hill. Out of desperation, they were using every mode of transportation.

SURESH BOJJA (ABOVE) THINKS THE AMBULANCE SAVED HIS LIFE AFTER A MOTORBIKE ACCIDENT AND SEVERE BEATING. THE SON OF LALITA ANAND (RIGHT) SAYS, “BECAUSE OF GVK, WE HAVE CARE.”
“Poor people are dying for simple reasons,” he says. “My heart throbs for that.”

Rao, who has been with EMRI since the start, is a bespectacled man with jet-black hair, a warm smile and an earnest demeanor, often leaning forward in his chair to reinforce his points. He is essentially EMRI’s chief medical officer, constantly looking for ways to improve patient care.

Rao says the system became possible because of two critical developments in India: the construction of a comprehensive road system and the communications revolution that has put 950 million cell phones into people’s hands, including those of the rural poor. “People may not have a square meal, but they have a mobile phone,” he says. “So it was a synergy of many technologies.”

WE WERE LOOKING FOR WHO IS BEST IN EMERGENCY MEDICINE AND WE DID A GOOGLE SEARCH AND FOUND STANFORD. AND THERE, WE FOUND DR. MAHADEVAN, WHICH MEANS GREAT GOD IN HINDI.

The number 108 was chosen for the toll-free service because it is considered an auspicious number in multiple religions prevalent in India. The service was launched on a small scale in Hyderabad, a sprawling mega-city of about 7 million people, in which gleaming malls and office buildings housing high-tech companies such as Google, Oracle and Cisco mingle with 16th-century Moghul monuments and the grit and decay of poor neighborhoods. The central call center there now serves the 83 million people in the states of Andhra Pradesh and Telangana.

EMRI has replicated the network in 15 states across a broad swath of this country of 1.2 billion, the second most populous in the world. It deploys five boat ambulances in the tea-producing state of Assam, in the country’s northeast region, where the Brahmaputra, one of Asia’s major rivers, snakes through the province. And there are ambulance rescues in the farthest reaches of the Himalayas, made possible by the construction of roads to access patients.

Each state contributes to the system, as does the federal government. Together they provided a total of $156 million in fi-
nancing in 2014 — the equivalent of 1 rupee (about 2 cents) per citizen per month, says Krishnam Raju, EMRI’s director. The system also depends on private philanthropy, with initial support provided by Ramalinga Raju, former chair of Satyam Computer Sciences. When he ran into financial trouble in 2009, the organizers turned to industrialist G.V.K. Reddy, who agreed to rescue the system, contributing $250 million to date through his family foundation. Reddy, 78, is a self-made billionaire, the son of a farmer, who has not forgotten his roots.

“I strongly believe in giving back to society by reaching out to the masses,” he says. “It couldn’t have been fulfilled better than providing emergency care and saving lives. It gives me immense satisfaction that EMRI 108 services … are reaching out to the poorest of the poor in rural areas.”

The funds are used to pay salaries and buy ambulances, designed and built in India to accommodate local needs. The vehicles are constructed differently from ambulances in the United States, as they include a side bench to carry as many as five or six family members along with the patient.

Though the government was able to supply needed equipment from the outset, India had no paramedics or emergency medical technicians to staff the vehicles, so officials began searching for a partner to help train an entirely new class of medical professional. That’s how Changavalli ended up in Mahadevan’s office.

“We were looking for who is best in emergency medicine and we did a Google search and found Stanford. And there, we found Dr. Mahadevan, which means great God in Hindi,” Rao says with a smile.

Mahadevan is a native of Oakland, California, but his parents emigrated from India, a connection EMRI officials hoped would endear the project to him. He began working as a consultant for the group in 2005, and by 2007 the School of Medicine had signed a formal agreement to develop an educational curriculum and train an initial group of 150 highly skilled paramedics and 30 paramedic instructors.

“The goal was to have them replace us as instructors,” Mahadevan tells Stanford students in a class on global entrepreneurship. He is a tall, lanky man with a gregarious nature who has won numerous awards for his teaching and his clinical expertise. In the early days of the project, he spent nearly as much time in India as he did in California, focused on training the new caregiver-educators.

“We saw an amazing transformation. These novice teachers became experts,” he says. “They devoured our teaching approach. ... The day our first group graduated in 2009 was one of the proudest days of my life.”

The Indian government also invested in educating a cadre of emergency medical technicians, who receive less training than paramedics but have the skills to manage the daily influx of medical emergencies. When an assessment found them lacking in certain subjects, Stanford physicians stepped in to supplement the EMT curriculum with refresher courses to improve their performance.

Peter D’Souza, MD, clinical assistant professor of emergency medicine, was one of the Stanford faculty who volunteered as a trainer, in part because of a personal experience, he says. He had seen the impact of the emergency-care
gap firsthand when a cousin in the south Indian metropolis of Bangalore suffered an injury to her spine in a traffic accident in the 1990s. “People picked her up and put her in the back of a rickshaw,” recalls D’Souza, whose parents are from India. “She had a broken spine and ended up paralyzed. My mother always said, ‘Had she been treated properly, she might be able to walk today.’”

PREPARING PARAMEDICS

IN A CLASSROOM AT EMRI HEADQUARTERS, ON THE NORTHERN OUTSKIRTS OF HYDERABAD, paramedic instructor Rafi Baigmirza is pounding on the chest of a patient in ventricular fibrillation, a dangerously abnormal heart rhythm. The “patient” in this case is a sophisticated manikin that coughs, screams and breathes to emulate real-life medical situations.

“It’s a chance to treat someone critically ill and make mistakes and learn from your mistakes so you can correct the situation in real life,” Mahadevan says of the simulation training.

In a neighboring classroom, Matt Strehlow, MD, clinical associate professor of emergency medicine at Stanford, is delivering a lecture on the basics of heart disease — the No. 1 killer in India — to 60 men and women, all second-semester paramedic students enrolled in the two-year training course. The students are often shy and tentative at first and have to be coached in how to establish a presence in chaotic situations, particularly roadside accidents, which tend to attract boisterous and unruly mobs of people who can interfere with treatment.

“You need to speak with your paramedic voice — be friendly and in charge,” Strehlow tells the group.

The chaos is evident on a recent August afternoon, when the EMTs respond to a call involving a 19-year-old college student who, in the course of turning left, was hit in the flank by another motorcyclist. The student was thrown from the bike and landed on the pavement, briefly losing conscious-ness. The EMTs hoist him into the ambulance, wrapping his injured right wrist in gauze and cutting open his right pant leg to splint a fractured limb. Several dozen onlookers gather, and there is much jostling and pushing as one gawker shoves a reporter aside so he can snap a photo of the action on his tablet computer.

Strehlow says that when the early crop of paramedics first began working in the field, they were an unknown quantity and often faced hostile crowds. He recalls one case in 2007 in Hyderabad in which a neighbor called 108 to report two children who had been tied up and abused.

“We arrive and there’s this huge crowd. The EMT looks at us and tells us to stay in the ambulance,” he says. “People were yelling and rocking the ambulance. They didn’t trust us. They didn’t understand. They were afraid.”

Today, however, the emergency responders are welcomed with open arms. Sometimes they deliver such good care that patients don’t want to leave the ambulance to enter the hospital, where treatment standards are highly variable, he says.

“It’s remarkable how they were able to turn the tide of public thought,” says Strehlow, the new director of Stanford Emergency Medicine International. “They are cheered. People trust the EMTs and that the system is working for them.”

In training the paramedics, the Stanford instructors had to tailor the curriculum to local needs, which are very different from those in the United States. For instance, about one-third of calls to the system, particularly in rural villages, are from pregnant women in labor, who traditionally deliver babies at home, often at great risk. In the past, the maternal mortality rate in India was very high, as women frequently died of complications, such as hemorrhage, infection or obstructed labor. In 1990, for every 100,000 women giving birth, 560 died, according to data from the World Health Organization, the World Bank and the United Nations. The Stanford team has since designed...
a specialized obstetric curriculum and helped create the country’s first protocols for obstetric care.

“For us, it’s like a bible, a commandment,” Rao says of the protocols. “We are very proud to bring international standards of care to our country with the help of Stanford.”

EMRI also established a separate call number, 102, for free transportation to and from the hospital for women in labor. It now deploys 3,000 ambulances in eight states specifically for this purpose. The maternal mortality rates have dropped significantly — to 190 deaths per 100,000 in 2013 — and Rao says he believes EMRI’s work has played a key role in helping save many women in labor.

The training curriculum also had to take into consideration other common medical problems in India, such as snakebites and pesticide poisonings. Drinking pesticide is a frequent method of suicide in rural villages, especially when the monsoon rains are sparse and crops fail; hopeless farmers see no other way out. Paramedics are now trained to administer atropine, a drug that counters the effect of these toxic chemicals.

Stanford physicians also learned that Indians aren’t prone to some of the medical issues that frequently confront emergency personnel in this country. For instance, peanut allergies, which are common in the United States, are rare in India, D’Souza says. When he presented a lecture on the subject to would-be paramedics, “most of the students didn’t even know what I was talking about.”

One of the plagues of the emergency system, particularly in urban areas, is roadside accidents, which account for 12 percent of calls. The mortality rate among traffic accident victims is immense in India, as few people wear safety helmets or take other precautions, and in the past, many failed to get care in time, Mahadevan says. Moreover, before the 108 system was introduced bystanders were
loath to become involved since accidents were the province of the police: They feared they’d be implicated in the injury and hauled off to jail, he says. As a result, victims often remained by the roadside, unattended.

“Now bystanders can call the emergency number and have a role in saving someone’s life,” he says.

THE HUB

THE HYDERABAD HUB FOR THE EMERGENCY SYSTEM IS A CALL CENTER THE SIZE OF TWO BASKETBALL COURTS, filled with a hum of voices and rhythmic tapping on computer keyboards as emergency responders in white coats answer the phone to 108 callers. More than 50 call operators, all fitted with headsets, are arrayed in circles inside blue and yellow cubicles that fill the cavernous space. A dashboard on the wall displays in red, yellow and green the number of calls waiting or active; officials are proud of the system’s record in responding to 96 percent of calls within the first ring.

The operators, who speak English, Hindi and Telugu, the local language, quickly gather essential details and enter these into a template on the computer screen: name, phone, location, chief complaint.

This call center alone responds to between 27,000 and 30,000 calls a day from residents in Andhra Pradesh and Telangana. Only about a quarter are true emergencies. The operators remind callers that the number is not to be used for idle chat; those who make repeated nuisance calls are warned they will be reported to the police if they continue to abuse the system.

It’s a far more sophisticated system than in the United States, where the 911 network is highly decentralized, with calls handled county by county according to variable standards, Mahadevan says. “They are very efficient, compared to us,” he says.

On a Thursday afternoon in August, an operator relays a call via mobile phone to emergency medical technician Banothu Mangilal, who has been waiting with two colleagues in one of the ambulances strategically placed around the city of Hyderabad. Mangilal, 28, who is from a poor family in the countryside, says he was inspired to sign up for EMT
training about three years ago after his mother suffered a hip fracture in an accident and got help through the system. The work, he says, is immensely satisfying.

“After a night shift of four or five cases, I can go home and tell my wife or parents how I have saved one person,” he says in Telugu through a translator.

On this day, the call involves an older woman who is unconscious. Because many homes lack specific addresses, Mangilal uses landmarks, such as temples or retail stores, to help locate the patient, who lives in a tumbledown neighborhood of cement-block apartment houses, where painted green balconies and blue awnings mix with a tangle of electrical wires and hanging laundry. He and his colleagues maneuver through a thicket of cars, trucks, motorcycles and rickshaws, arriving at the second-floor unit — a dark, closet-sized room occupied by a single bed — where 72-year-old Lalita Anand lies in a brown dress, eyes closed, unresponsive. Her son, Ranesh Anand, had arrived that morning from Mumbai to discover his mother, a recent cancer patient, in a terrible state, unable to speak. He called 108. A strong odor in the room greets the EMTs, who don facemasks as family members scurry to get the patient ready to go.

A brief exam reveals the likely source of her distress: a baseball-sized bedsore on her back that has become infected and may have led to sepsis, a potentially fatal condition, says Strehlow, who is observing the EMTs today. The EMTs give the patient oxygen and start an intravenous line for fluids, then gently lift her onto a backboard and maneuver her down a narrow stairwell.

Three family members climb into the ambulance, which arrives at Prime Hospital, a teeming, well-appointed private facility requested by the family. EMRI has signed agreements with many private hospitals that will treat patients free of charge for the first 24 hours. Then the patient may stay there or move to a government facility, where care is free. Many families choose the private option, even though they may have to bankrupt themselves to pay the bills, because they know the care will be better.

In an emergency room bay, Lalita Anand begins to revive. Her eyes open and she responds to questions. Her relatives are beaming.

“Because of GVK, we have care,” the son says. “Everything is normal. … We congratulate them and now we have to pray to God for her to recover. They have provided excellent service. We will remember it for a long time.”

TRACKING TRENDS

Because EMRI’s computerized system can capture massive quantities of data, researchers for the first time can track health-care trends and spot problems that need to be addressed. For instance, in one study, scientists from Stanford and EMRI tracked all patients in Andhra Pradesh in July 2009 who called with complaints of chest pain — a total of 585 individuals. They found an “alarming early mortality” rate, with 23.2 percent dead within a month. Many were arriving too late to the hospital to be saved, Mahadevan says.

As a result of the study, published in 2010 by the American Academy of Emergency Medicine, most ambulances now carry defibrillators to revive patients in cardiac arrest.

In another study, the scientists looked at more than 1,000 adults and children suffering seizures — the most common neurologic emergency in India — over a two-month period in the state. They found that only 14 percent of these patients were given anti-seizure medications, and 5 percent were dead within a week. The ambulance procedures lacked instructions for patients with seizures, so the Stanford team corrected that with new guidelines and made sure that all ambulances carried anti-seizure medications, typically benzodiazepines.

Currently, the Stanford team is working with EMRI to collect data on burns, which are “horrendously common and
AND

VIRUS

MAKES FOUR

WE MAY BE INFECTED — AND PROTECTED — FROM OUR EARLIEST DAYS OF DEVELOPMENT

The next time you start to feel special, keep in mind that much of your DNA isn't even yours. In fact, your genome is littered with the ancient corpses of viral invaders of hundreds (or even millions) of years ago. Basically, each of us is just a giant junk heap.

If you find that dispiriting, here’s another bit of unsettling news: Some of these skeletons come back to life during very early human development. The viral DNA makes viral proteins, which assemble themselves into something that looks suspiciously like infectious viral particles. • “It’s both fascinating and a little creepy,” says Joanna Wysocka, PhD, Stanford associate professor of developmental biology and of chemical and systems biology. “We can’t say yet whether these viral particles can be infectious, but regardless of whether they are, viral proteins within a cell are rarely completely inert.” • Wysocka described the phenomenon in a paper published earlier this year in *Nature*. Graduate student Edward Grow was the study’s first author. • The finding raises questions as to who, or what, is really pulling the strings during human embryogenesis. Grow and Wysocka have found that these viral proteins are well-placed to manipulate some of the earliest steps in our development

BY KRISTA CONGER

PHOTOGRAPH BY MISHA GRAVENOR

JOANNA WYSOCKA FOUND VIRAL PROTEINS IN HUMAN EMBRYONIC CELLS.
by affecting gene expression and even possibly protecting the embryo’s cells from further viral infection.

It’s unclear, however, whether we are watching an ongoing battle between viruses and humans or the outcome of an uneasy truce hashed out over tens of thousands of years of evolution.

“Does the virus selfishly benefit by switching itself on in these early embryonic cells?” wonders Grow. “Or is the embryo instead commandeering the viral proteins to protect itself? Can they both benefit? That’s possible, but we don’t really know.”

WHEN GENES JUMP

The researchers didn’t start out looking for reanimated zombie viruses. They were mostly interested in understanding the earliest stages of human embryonic development: how a newly fertilized egg no bigger than the period at the end of this sentence becomes a squalling newborn with limbs, hair, fingers and a hefty set of lungs with which to manipulate the emotions and actions of nearby parents.

Researchers have known for nearly six decades that nearly every cell in the human body contains 23 pairs of chromosomes — stubby bundles of DNA strings that carry the instructions to make every protein in the body. This DNA makes up what’s known as our genome, and it’s kept within a special control center inside the cell called the nucleus. With a few exceptions, all cells in your body contain the same genome, but they use the encoded instructions to make different tissues and organs.

It’s somewhat like how a good cook can use a set of cookbooks and a well-stocked pantry to make an omelet, or a cake, or a succulent beef roast. Ingredients and timing are everything. All these foods are tasty, but you wouldn’t want a roast for dessert or a cake for the main course of your holiday dinner.

A cell relies on the sequential and coordinated expression of genes in the genome for its molecular recipes. Specific sequences in the DNA are copied into RNA in a process called transcription. For the most part, these RNA messages then leave the nucleus and travel to protein-making machinery called ribosomes in the cell’s cytoplasm. (Other RNA molecules perform regulatory functions that direct the expression of other genes in the genome.) At the ribosome, the protein is assembled and sent off on its merry way to direct the function or development of the cell.

Wysocka and Grow were interested in the regulatory mechanisms within an early embryo that control which genes are made into RNA and proteins, and at which times during development. They homed in on a mobile genetic element called a transposon. Transposons are short bits of DNA that in their active, mobile form can insert (and re-insert) themselves over and over into the host DNA, resulting in hundreds or even thousands of copies hiding in our genome. Altogether, they make up about half of our genome. However, with time they accumulate mutations and rarely encode protein-making instructions themselves. Recently, though, they have been shown to play an important regulatory role in the expression of nearby genes.

You may remember transposons as the “jumping genes” that garnered Barbara McClintock the Nobel Prize in Physiology or Medicine in 1983. Unfortunately, her discovery, made in the 1950s, was largely ignored for decades. Until the full effect of McClintock’s groundbreaking research was realized some 30 years later, transposons were considered to be genetic junk.

Think of transposon jumping as reorganizing or flipping the order of segmented pieces of track in a toy train set. Depending on the configuration or specific purpose of each section — does it have an off-shoot to direct the train off the route, or a stop signal to halt its progress? — the location and orientation of the newly inserted sections can matter a great deal. As McClintock showed, the transposon’s brand of genetic shenanigans can affect the color and pattern of kernels on a cob of corn.

But when Grow began to investigate when, how and which transposons were activated in human development, he found something surprising.

STEALTH VIRUSES

“There was something very interesting, and very specific, going on,” says Wysocka. “Those transposons that were particularly dynamic, activating at very specific times early in development, were made up of endogenous retroviruses.”

A retrovirus is a special category of transposon — one with nonhuman origins. About 8 percent of our genome is made up of these ancient retroviral sequences left behind during past infections hundreds of thousands of years ago. They’re referred to as endogenous because they are within our DNA, as opposed to the exogenous viruses we might contract from another human being.

In an active infection, retroviruses insert their genetic material into the genome of the host cell for later reactivation. In this stealth mode, the virus bides its time, taking advantage of cellular DNA replication to spread to each of an infected cell’s progeny every time the cell divides. HIV is one well-known example of a retrovirus that infects humans.
When a retrovirus infects a germ cell, which makes sperm and eggs, or infects a very early-stage embryo before the germ cells have arisen, the viral DNA is passed along to future generations. Over evolutionary time, these viral genomes typically become mutated and inactivated. One retrovirus, however, called HERVK, infected humans repeatedly until relatively recently — within about 200,000 years. Much of HERVK’s genome is still snuggled, intact, in each of our cells.

“HERVK is an interesting exception to most other endogenous retroviruses that infected primates like ourselves,” says Wysocka. “It’s evolutionarily younger and, in the case of more than 100 insertions into our genome, it has retained its protein-coding potential.”

Most of these viral sequences are inactive in mature cells, but recent research in other labs has shown that DNA from a retrovirus called HERVH, which is related to HERVK, is made into RNA at specific points in human embryonic development. This happens due to a phenomenon called hypomethylation, in which a cell sheds chemical tags called methyl groups that normally speckle its DNA. These methyl groups are a key way that a cell silences the expression of unnecessary genes. It wouldn’t do to have a skin cell suddenly start churning out digestive enzymes, for example.

“During development, there is a global wave of hypomethylation of the genome, which provides a window of opportunity for reactivation of previously silent elements,” says Wysocka.

This shedding of methyl groups is one way egg cells gain the developmental potential necessary to become all the tissues in the body. It also occurs sometimes in cancer cells, permitting them to attain new, potentially dangerous functions during the course of the disease. Furthermore, as the previous research showed, it releases recently acquired transposons and retroviruses for expression by the cellular machinery. Until now, however, it wasn’t known whether the cell actually used the RNA sequences made from ancient retroviral DNA to make viral proteins that could affect its function and development.

“We started looking at the transcription of these transposable elements early in development and found that there’s something very interesting and very specific going on. Different transposons are activated during different cellular states — so much so that it’s possible to identify the state a cell is in just by which transposons have been activated,” Wysocka says. “Endogenous retroviral elements,” like HERVK, “are particularly dynamic.”

Grow and Wysocka found that, in 3- to 4-day-old embryos, some HERVK viruses are transcribed into RNA. This viral activation coincides with the activation of other key human genes in the embryo. Then, researchers teamed up with Shawn Chavez, PhD, and Mark Wossidlo, PhD, two post-doctoral scientists from the lab of Renee Reijo Pera, PhD, a former Stanford professor of obstetrics and gynecology and former director of the Center for Human Embryonic Stem Cell Research and Education, to visualize viral proteins in the human embryos using antibodies labeled with fluorescent dyes. Finally, the researchers used electron microscopy to observe what appear to be intact viral particles in the human blastocyst, the hollow ball of cells that arises within five to six days after fertilization. They verified that the particles

‘OUR “JUNK DNA,” INCLUDING SOME VIRAL GENES, IS RECYCLED FOR DEVELOPMENT IN THE FIRST FEW DAYS AND WEEKS OF LIFE. THE QUESTION IS, WHAT IS IT DOING THERE?’
were made up of viral proteins by tagging them with gold-labeled antibodies. (Gold's density appears as distinct black spots when viewed with an electron microscope.).

“When we looked at these human blastocysts, we saw they were packed full of viral proteins,” says Wysocka. “This was true for every blastocyst we looked at. Early human development clearly proceeds in the presence of viral proteins.”

When asked why these proteins haven’t been found before, Wysocka says, “I don’t know. People simply haven’t looked. Nobody really thought, ‘Well, let’s see if they actually make proteins in human embryos,’ even though such proteins have been seen before in germ cell tumors and cancer cells that transcriptionally reactivate HERVK.”

Although the viral proteins seem to assemble themselves into viral particles, it’s unclear whether they are capable of infecting other cells. That’s one thing the researchers would like to test. What they do know is that one of the proteins made by HERVK is a viral protein called Rec. When a cell is first infected by HERVK, Rec binds to viral RNA particles and escorts them to the ribosomes in the cells’ cytoplasm to be made into proteins. These viral proteins are then assembled into new viral particles, which are released to infect more cells.

Wysocka and Grow found that Rec affects the expression of more than just viral genes. In collaboration with the laboratory of Howard Chang, MD, PhD, a professor of dermatology at Stanford and a Howard Hughes Medical Institute investigator, they found it also binds to many RNAs made from human genes and affects the degree to which they interact with the cell’s ribosomes. Furthermore, its presence stimulates the cell to increase the amount of a surface-bound protein that protects it from subsequent viral invasion — a kind of molecular “get off my lawn” sign that firmly stakes a virus’ claim to the cell. Many questions remain, however, as to how long this protection may last, or what could be its purpose.

**TUG OF WAR**

So, who’s in charge here? Us or the viruses? Or is there no longer any distinction? There’s certainly been plenty of evidence showing that humans are far from free operators when it comes to, well, pretty much anything. Our bodies are teeming masses of bacteria, viruses and even fungi that are collectively known as the microbiome. Many of these microorganisms, which are 10 times more numerous than our own cells, are essential to a healthy life, such as the gut bacteria that help us digest our food.

“What we’re learning now is that our ‘junk DNA,’ including some viral genes, is recycled for development in the first few days and weeks of life,” says Pera, who is now on the faculty of Montana State University. “The question is, what is it doing there?”

It’s not clear whether this sequence of events is the result of thousands of years of co-existence, a kind of evolutionary symbiosis, or if it represents an ongoing battle between humans and viruses. Regardless, it’s clear the fates of both virus and human cell are intertwined within days of conception.

Grow and Wysocka are now doubling down on their efforts to understand whether and how the viral transposons themselves affect the regulation of human gene expression. Do they enhance the expression of our own genes at particular times during development or in particular cells? More to the point: Who are the real cooks in our genomic kitchens?

“There is always a tug of war between a host and a virus,” says Wysocka. “Infection of our ancestors with HERVK was an accident of evolution. Regardless of whether the effect of this infection is positive or negative from the natural-selection standpoint, the virus clearly has an impact. We believe that the virus is likely to influence and fine-tune many early developmental pathways specific to primates. They may even affect those that make us uniquely human.”

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**FEATURE**

Go to bed

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they might shrug off if they were fully rested, she says.

“Based on prior research, we have theorized that sleep disturbances may result in difficulty regulating emotional information, and this may lower the threshold for suicidal behaviors among at-risk individuals,” says Bernert, an instructor in psychiatry and behavioral sciences. Now she’s studying whether a brief nondrug treatment for insomnia reduces depression and risk for suicide.

Sleep deprivation also has been shown to lower inhibitions among both adults and teens. In the teen brain, the frontal lobe, which helps restrain impulsivity, isn’t fully developed, so teens are naturally prone to impulsive behavior.

“When you throw into the mix sleep deprivation, which can also be disinhibiting, mood problems and the normal impulsivity of adolescence, then you have a potentially dangerous situation,” Joshi says.

**SOME SCHOOLS SHIFT**

Given the health risks associated with sleep problems, school districts around the country have been looking at one issue over which they have some con-
trol: school start times. The trend was set by the town of Edina, Minnesota, a well-to-do suburb of Minneapolis, which conducted a landmark experiment in student sleep in the late 1990s. It shifted the high school’s start time from 7:20 a.m. to 8:30 a.m. and then asked University of Minnesota researchers to look at the impact of the change. The researchers found some surprising results: Students reported feeling less depressed and less sleepy during the day and more empowered to succeed. There was no comparable improvement in student well-being in surrounding school districts where start times remained the same.

With these findings in hand, the entire Minneapolis Public School District shifted start times for 57,000 students at all of its schools in 1997 and found similarly positive results. Attendance rates rose, and students reported getting an hour’s more sleep each school night — or a total of five more hours of sleep a week —countering skeptics who argued that the students would respond by just going to bed later.

Other studies have reinforced the link between later start times and positive health benefits. One 2010 study at an independent high school in Rhode Island found that after delaying the start time by just 30 minutes, students slept more and showed significant improvements in alertness and mood. And a 2014 study in two counties in Virginia found that teens were much less likely to be involved in car crashes in a county where start times were later, compared with a county with an earlier starting bell.

Bolstered by the evidence, the American Academy of Pediatrics in 2014 issued a strong policy statement encouraging middle and high school districts across the country to start school no earlier than 8:30 a.m. to help preserve the health of the nation’s youth. Some districts have heeded the call, though the decisions have been hugely contentious, as many consider school schedules sacrosanct and cite practical issues, such as bus schedules, as obstacles.

In Fairfax County, Virginia, it took a decade of debate before the school board voted in 2014 to push back the opening school bell for its 57,000 students. And in Palo Alto, where a recent cluster of suicides has caused much communitywide soul-searching, the district superintendent issued a decision in the spring, over the strenuous objections of some teachers, students and administrators, to eliminate “zero period” for academic classes — an optional period that begins at 7:20 a.m. and is generally offered for advanced studies.

Certainly, changing school start times is only part of the solution, experts say. More widespread education about sleep and more resources for students are needed. Parents and teachers need to trim back their expectations and minimize pressures that interfere with teen sleep. And there needs to be a cultural shift, including a move to discourage late-night electronic use, to help youngsters gain much-needed rest.

“At some point, we are going to have to confront this as a society,” Carskadon says. “For the health and well-being of the nation, we should all be taking better care of our sleep, and we certainly should be taking better care of the sleep of our youth.”

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The National Suicide Prevention Life-line toll-free number, 1-800-273-TALK, is available 24/7 in the United States.
adoption of skin-to-skin care in other parts of India, using the same community-based principles they developed in Shivgarh. And Darmstadt has integrated the emphasis on community systems and culture into his more recent work on promoting gender equity and empowering women and girls. One example, says Darmstadt, is a project with the Inter-American Development Bank and the government in Honduras that sought to reduce maternal deaths by having women give birth in hospitals or clinics. Yet the team realized they needed to broaden the scope of efforts to include nutrition, family planning and girls’ education, rather than simply urging pregnant women to head to the hospital.

“As I’ve gone along in my career, I’ve increasingly felt the importance of taking a holistic approach to people’s lives, to developing an understanding of the ecosystem in which people live and what it is that’s important to them, and using that to develop solutions with them, rather than coming in with preconceived ideas about what the problems are and what the solutions are,” he says.

But he knows that one piece currently missing in many efforts to help newborns is a focus on gender equity — because the rampant marginalization and neglect of women and girls is not only a rights issue, it’s a health issue for women and men, girls and boys.

During the Shivgarh project, the team was silent about gender, hoping that by treating each infant equally they would model gender-neutral behavior and thus improve care for girls, who are often neglected. This did happen, but Darmstadt says he has since realized that’s not enough. Gender inequality can be as blatant as female infanticide, but it can also involve more subtle distinctions such as feeding girls differently or taking them to less qualified or less costly health-care providers, he says. To ensure that all babies are treated equally and slash the newborn mortality rate, women and girls must be empowered. That may include formal education, literacy training, information about family planning, working with men and boys on equitable decision-making and control over resources, and more. “It’s really important that we address those inequalities to see major advances in maternal health as well as in many other areas of health and community development,” he says.

David Stevenson, MD, a professor of pediatrics at Stanford who worked to recruit Darmstadt, agrees. “If you make a change that is impactful for girls and women of childbearing age, then you can impact the values of the entire society.”

And to truly help every newborn, efforts will have to penetrate into some of the world’s most dangerous areas, Darmstadt says. These countries — Democratic Republic of the Congo, Pakistan, Sudan, Afghanistan and others — have the world’s highest rates of newborn deaths, but their public health problems have been overshadowed by ongoing conflict and instability. Without a community-centric focus, projects to help newborns in these countries are bound to fail — and could endanger health-care workers, he says.

“The real lesson is the program has to be matched to the local situation and local needs,” Darmstadt says. “In public health, we often don’t take enough care in that design process.”

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FEATURE
India’s medical miracle
CONTINUED FROM PAGE 49
often very severe — a pretty big challenge,” Strehlow says. According to the WHO, more than a million people are moderately or severely burned in India every year, compared with 40,000 patients with burns needing hospitalization in the United States in 2008 (the latest figures available).

Indian women typically cook on gas cooktops, and their loose-fitting nylon saris may accidentally brush against the flames, he says. But tragically, many burns are intentionally inflicted by the patient, a partner or another individual, says Jennifer Newberry, MD, JD, an instructor in emergency medicine who is leading the study.

Newberry decided to do the study after seeing some figures from a previous study of burn patients who called the 108 line. Her preliminary analysis of a sample of 434 burn patients who contacted the service over a 90-day period shows nearly half of all burns were intentionally inflicted. Most of those with intentional burns were young married women.

The overall mortality rate for burn patients is high, with 69 percent dying within a month, Newberry’s early analysis shows. By contrast, in the United States, most burn victims survive, even if their burns cover as much as 90 percent of the body, Strehlow says. Among other things, the researchers are looking at survival rates at both public and private hospitals and the levels of care provided.
IMPROVING PHYSICIAN SKILLS

Now that patients are arriving in large numbers at hospital emergency rooms, the hospitals are under pressure to improve the quality of care. But this remains an enormous challenge in a country where the concept of emergency care is very new and fewer than 1,000 emergency physicians practice.

At Gandhi Hospital, a government-run facility in the central city here, an ambulance pulls up to the emergency room door on a Friday afternoon. Medical professionals deliver a patient on a gurney, his blue jeans and T-shirt spattered with red and his right arm in a blood-soaked bandage. The patient, a man in his 20s found injured along the roadside, is still conscious but in severe shock due to blood loss from a gaping wound on his right hand.

EMTs wheel him into the emergency room, where caregivers begin to irrigate the wound, which drips blood over a trash can, and hook him up to an intravenous line. Strehlow, who has been observing the action, says the patient could survive if he gets a transfusion and manages to avoid infection in this hospital, where the walls are peeling plaster, the bed linens are stained and a pile of medical waste and garbage lurks outside the window.

It’s a grim scene where about a dozen patients, many in critical condition, lie on gurneys awaiting care from the only physician in attendance. A man in the corner with a bony chest is heaving in great distress; he desperately needs oxygen, but the staff isn’t there to deliver it.

Despite the chaos, Strehlow says things have marginally improved. About eight years ago, when he visited the same emergency room, he saw two women on gurneys in severe respiratory distress, dangerously close to death, without any aid in sight.

In the back room, Strehlow says he found a physician, feet up on the desk. The physician told him, “What do you want me to do? I’m an ophthalmologist. I don’t know what to do,” Strehlow recalls.

At least now some patients are starting to get urgent medical attention as the public clamors for hospitals to respond.

“Now that the concept of emergency care has been introduced, the public is applying external pressure for desperately needed care,” he says.

To help meet the demand, Stanford and EMRI are working to beef up the skills of the generalists who staff emergency rooms, particularly in the government-run district hospitals in rural areas. They have developed a short course for these physicians on how to triage emergencies in both adults and children and how to assess a patient’s condition when expensive tools such as MRI and CT machines are unavailable, Rao says.

EXPANDING HORIZONS

That is just one of EMRI’s initiatives as it pursues its ambitious agenda. The service aims to double the number of ambulances to 20,000 within the next five years and reduce the average response time in urban areas from 15 minutes to 10 minutes, director Krishnam Raju says. And it plans to extend the service to the entire country and beyond. At the Aug. 15 celebration, chairman Reddy said that in addition to the Sri Lanka expansion, he has approached Indonesia and Thailand to introduce the model there as well.

In India itself, Raju says he believes the 108 service will add at least another five years to the current 67-year life expectancy. And EMRI will continue to work in partnership with Stanford as it expands and brings India into the modern age of emergency care.

“We look forward to another decade of continuing to improve care,” Mahadevan says. “It’s only in its infancy. Over time, I’m confident it’s going to deliver the same level of care available in other countries.” SM

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BRAIN TRUST
HOW ONE FAMILY’S TUMOR DONATION INSPIRED OTHERS AND LAUNCHED RESEARCH

On her son’s first day as a brain tumor patient at Lucile Packard Children’s Hospital Stanford, Danah Jewett asked one of his doctors if her family could donate 5-year-old Dylan’s organs to other children when he died. • Most organs from cancer patients can’t be transplanted, the pediatric neuro-oncologist, Michelle Monje, MD, PhD, explained. But the Jewetts could make an even bigger difference by giving Dylan’s tumor to Stanford for research, a donation with the potential to fill a gaping hole in the science of childhood cancer. • Surprised, Dylan’s parents said yes. • After Dylan’s death on Jan. 8, 2009, Monje and her colleagues transformed his tumor into the first cell culture of its type anywhere in the world. A few months later, a Stanford Medicine story about the Jewetts’ gift inspired more families to make similar donations, further boosting the research.

Dylan had diffuse intrinsic pontine glioma, which grows in the brain stem region that controls breathing and heartbeat, tangling its cancerous cells with healthy cells “like a sweater knitted of multicolored yarn,” says Monje. It’s rare, striking a few hundred school-aged children in the United States each year, but not rare enough. Of every 100 patients, 99 die within five years of diagnosis. And DIPG’s dismal prognosis has not improved in 40 years.

Monje, now an assistant professor of neurology, was motivated to study the disease by the plight of a young patient she cared for while still a medical student. But when she began her work, she hit a roadblock: Because of its location, the tumor isn’t usually biopsied. There were no DIPG cells to examine in the lab.

In 2008, when Monje received approval for a protocol to collect tumor tissue from recently deceased DIPG patients for research, she worried about how parents of dying children would feel about being asked to donate the tissue. Shortly thereafter, Dylan came to Stanford, and his parents wanted to help doctors change the course of a disease his dad, John, calls “a death sentence for kids.”

Their generous donation and openness about sharing their story made a difference: Twenty-one families, many of whom learned of the need for donations by reading Dylan’s story in Stanford Medicine, have now donated tumor tissue to Monje’s lab.

With the donated tissue, Monje’s team created the first cell line and mouse model of the tumor, which they have shared with scientists around the world. They’ve identified a candidate cell of origin for DIPG, learned that the tumor hijacks part of the brain’s normal mechanism for neuroplasticity to promote its own growth, and identified an FDA-approved drug that extends the lives of mice with the disease. The team is now planning a clinical trial of this drug, panobinostat, to see if it will also help children.

Danah later met one family that donated tumor tissue after reading the story about Dylan: “I thought, ‘Wow, this really encouraged another family to do this,’” she says. “It was a really good feeling.”

Many families of DIPG patients have also raised money for Monje’s research, contributing a total of more than $1 million to date.

“The story doesn’t end when Dylan died,” Danah says. “It feels good to know that my child’s life wasn’t just those five years. He’s continuing to make a difference.” — ERIN DIGITALE
Faculty at Stanford’s Hasso Plattner Institute of Design, aka the d.school, are devoted to instilling creativity in their students. But how do they know they’ve succeeded? • Enter a professor at the School of Medicine, an MRI machine and a little inspiration from the board game Pictionary. • “Creativity is an incredibly valued human attribute in every single human endeavor,” says professor of radiology and of psychiatry and behavioral sciences Allan Reiss, MD, who collaborated with d.school researchers who wanted to measure the attribute objectively. The team asked adults whose brain activity was being monitored by fMRI to draw words like “vote,” “exhaust” and “salute.” They then had the subjects rate the difficulty of illustrating each word. Later, the investigators graded the drawings on five-point scales for appropriateness and for creativity.

Words the subjects found more difficult were associated with increased activity in the left prefrontal cortex, an executive-function center involved in attention and evaluation. But high creativity scores were associated with low activity in the executive-function center and higher activation in the cerebellum, a structure in the back of the brain that is typically thought of as the body’s practice-makes-perfect, movement-coordination center.

The heightened activity in the cerebellum and its association with high creativity scores were unexpected. The researchers speculate that the cerebellum may be able to subconsciously refine all new types of behavior acquired by the more frontally located cortical regions — not just movement. Other studies show that the human cerebellum has robust connections not only to the motor cortex, but to other parts of the cortex as well. “It’s likely that the cerebellum is an important coordination center for the rest of the brain, allowing other regions to be more efficient,” says Reiss, the senior author of the study, which appeared in May in Scientific Reports.

“As our study also shows, sometimes a deliberate attempt to be creative may not be the best way to optimize your creativity,” Reiss says. “While greater effort to produce creative outcomes involves more activity of executive-control regions, you actually may have to reduce activity in those regions in order to achieve creative outcomes.”

The bottom line: Don’t try too hard to be creative, says lead author Manish Saggar, PhD, an instructor in psychiatry who teaches at the d.school. “The more you think about it, the more you mess it up.”

— BRUCE GOLDMAN